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<b>(21) International Application Number:</b> PCT/US94/05739 <b>(22) International Filing Date:</b> 7 June 1994 (07.06.94) <b>(30) Priority Data:</b> 073,028                      7 June 1993 (07.06.93)                      US <b>(71) Applicant:</b> DUKE UNIVERSITY [US/US]; Erwin Road, Durham, NC 27706 (US). <b>(72) Inventors:</b> BOLOGNESI, Dani, P.; 17 Harvey Place, Durham, NC 27705 (US). MATTHEWS, Thomas, J.; 5906 Newhall Road, Durham, NC 27713 (US). WILD, Carl, T.; 1702 B Vista Street, Durham, NC 27701 (US). BARNEY, Shaen, O'Lin; 106 Branchway Road, Cary, NC 27502 (US). LAMBERT, Dennis, M.; 101 Centerville Court, Cary, NC 27513 (US). PETTEWAY, Stephen, R., Jr.; 203 Le Gault Drive, Cary, NC 27513 (US). <b>(74) Agents:</b> CORUZZI, Laura, A. et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, UA, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SYNTHETIC PEPTIDE INHIBITORS OF HIV TRANSMISSION  <b>(57) Abstract</b>  The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP-178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1 <sub>LAI</sub> gp41 protein, and fragments, analogs and homologs of DP-178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.		

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SYNTHETIC PEPTIDE INHIBITORS OF HIV TRANSMISSION1. INTRODUCTION

The present invention relates to DP-178 (SEQ ID:1), a peptide corresponding to amino acids 638 to 673 of the HIV-1<sub>LAI</sub> transmembrane protein (TM) gp41, and portions, analogs, and homologs of DP-178 (SEQ ID:1), all of which exhibit anti-viral activity. Such anti-viral activity includes, but is not limited to, the inhibition of HIV transmission to uninfected CD-4<sup>+</sup> cells. Further, the invention relates to the use of DP-178 (SEQ ID:1) and DP-178 fragments and/or analogs or homologs as inhibitors of human and non-human retroviral, especially HIV, transmission to uninfected cells. Still further, the invention relates to the use of DP-178 as a HIV subtype-specific diagnostic. The present invention also relates to antiviral peptides analogous to DP-107, a peptide corresponding to amino acids 558 to 595 of the HIV-1<sub>LAI</sub> transmembrane protein (TM) gp41, that are present in other enveloped viruses. The present invention further relates to methods for identifying antiviral compounds that disrupt the interaction between DP-178 and DP-107, and/or between DP-107-like and DP-178-like peptides. The invention is demonstrated by way of a working example wherein DP-178 (SEQ ID:1), and a peptide whose sequence is homologous to DP-178 are each shown to be potent, non-cytotoxic inhibitors of HIV-1 transfer to uninfected CD-4<sup>+</sup> cells. The invention is further demonstrated by working examples wherein peptides having antiviral and/or structural similarity to DP-107 and DP-178 are identified.

## 2. BACKGROUND OF THE INVENTION

### 2.1. THE HUMAN IMMUNODEFICIENCY VIRUS

The human immunodeficiency virus (HIV) has been implicated as the primary cause of the slowly degenerative immune system disease termed acquired  
5 immune deficiency syndrome (AIDS) (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo, R. et al., 1984, Science 224:500-503). there are at least two distinct types of HIV: HIV-1 (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo R. et al., 1984,  
10 Science 224:500-503) and HIV-2 (Clavel, F. et al., 1986, Science 233:343-346; Guyader, M. et al., 1987, Nature 326:662-669). Further, a large amount of genetic heterogeneity exists within populations of each of these types. Infection of human CD-4<sup>+</sup> T-  
15 lymphocytes with an HIV virus leads to depletion of the cell type and eventually to opportunistic infections, neurological dysfunctions, neoplastic growth, and ultimately death.

HIV is a member of the lentivirus family of  
20 retroviruses (Teich, N. et al., 1984, RNA Tumor Viruses, Weiss, R. et al., eds., CSH-Press, pp. 949-956). Retroviruses are small enveloped viruses that contain a diploid, single-stranded RNA genome, and replicate via a DNA intermediate produced by a  
25 virally-encoded reverse transcriptase, an RNA-dependent DNA polymerase (Varmus, H., 1988, Science 240:1427-1439). Other retroviruses include, for example, oncogenic viruses such as human T-cell leukemia viruses (HTLV-I,-II,-III), and feline  
30 leukemia virus.

The HIV viral particle consists of a viral core, composed of capsid proteins, that contains the viral RNA genome and those enzymes required for early  
35 replicative events. Myristylated Gag protein forms an



outer viral shell around the viral core, which is, in turn, surrounded by a lipid membrane envelope derived from the infected cell membrane. The HIV envelope surface glycoproteins are synthesized as a single 160 Kd precursor protein which is cleaved by a cellular protease during viral budding into two glycoproteins, gp41 and gp120. gp41 is a transmembrane protein and gp120 is an extracellular protein which remains non-covalently associated with gp41, possibly in a trimeric or multimeric form (Hammarskjold, M. and Rekosh, D., 1989, Biochem. Biophys. Acta 989:269-280). HIV is targeted to CD-4<sup>+</sup> cells because the CD-4 cell surface protein acts as the cellular receptor for the HIV-1 virus (Dalglish, A. et al., 1984, Nature 312:763-767; Klatzmann et al., 1984, Nature 312:767-768; Maddon et al., 1986, Cell 47:333-348). Viral entry into cells is dependent upon gp120 binding the cellular CD-4<sup>+</sup> receptor molecules (McDougal, J.S. et al., 1986, Science 231:382-385; Maddon, P.J. et al., 1986, Cell 47:333-348) and thus explains HIV's tropism for CD-4<sup>+</sup> cells, while gp41 anchors the envelope glycoprotein complex in the viral membrane.

## 2.2. HIV TREATMENT

HIV infection is pandemic and HIV associated diseases represent a major world health problem. Although considerable effort is being put into the successful design of effective therapeutics, currently no curative anti-retroviral drugs against AIDS exist. In attempts to develop such drugs, several stages of the HIV life cycle have been considered as targets for therapeutic intervention (Mitsuya, H. et al., 1991, FASEB J. 5:2369-2381). For example, virally encoded reverse transcriptase has been one focus of drug development. A number of reverse-transcriptase-

targeted drugs, including 2',3'-dideoxynucleoside analogs such as AZT, ddI, ddC, and d4T have been developed which have been shown to be active against HIV (Mitsuya, H. et al., 1991, Science 249:1533-1544). While beneficial, these nucleoside analogs are not  
5 curative, probably due to the rapid appearance of drug resistant HIV mutants (Lander, B. et al., 1989, Science 243:1731-1734). In addition, the drugs often exhibit toxic side effects such as bone marrow suppression, vomiting, and liver function  
10 abnormalities.

Attempts are also being made to develop drugs which can inhibit viral entry into the cell, the earliest stage of HIV infection. Here, the focus has thus far been on CD4, the cell surface receptor for  
15 HIV. Recombinant soluble CD4, for example, has been shown to inhibit infection of CD-4<sup>+</sup> T-cells by some HIV-1 strains (Smith, D.H. et al., 1987, Science 238:1704-1707). Certain primary HIV-1 isolates, however, are relatively less sensitive to inhibition  
20 by recombinant CD-4 (Daar, E. et al., 1990, Proc. Natl. Acad. Sci. USA 87:6574-6579). In addition, recombinant soluble CD-4 clinical trials have produced inconclusive results (Schooley, R. et al., 1990, Ann. Int. Med. 112:247-253; Kahn, J.O. et al., 1990, Ann.  
25 Int. Med. 112:254-261; Yarchoan, R. et al., 1989, Proc. Vth Int. Conf. on AIDS, p. 564, MCP 137).

The late stages of HIV replication, which involve crucial virus-specific secondary processing of certain viral proteins, have also been suggested as possible  
30 anti-HIV drug targets. Late stage processing is dependent on the activity of a viral protease, and drugs are being developed which inhibit this protease (Erickson, J., 1990, Science 249:527-533). The

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clinical outcome of these candidate drugs is still in question.

Attention is also being given to the development of vaccines for the treatment of HIV infection. The HIV-1 envelope proteins (gp160, gp120, gp41) have been shown to be the major antigens for anti-HIV antibodies present in AIDS patients (Barin, et al., 1985, Science 228:1094-1096). Thus far, therefore, these proteins seem to be the most promising candidates to act as antigens for anti-HIV vaccine development. To this end, several groups have begun to use various portions of gp160, gp120, and/or gp41 as immunogenic targets for the host immune system. See for example, Ivanoff, L. et al., U.S. Pat. No. 5,141,867; Saith, G. et al., WO 92/22,654; Shafferman, A., WO 91/09,872; Formoso, C. et al., WO 90/07,119. Clinical results concerning these candidate vaccines, however, still remain far in the future.

Thus, although a great deal of effort is being directed to the design and testing of anti-retroviral drugs, a truly effective, non-toxic treatment is still needed.

### 3. SUMMARY OF THE INVENTION

The present invention relates to DP-178 (SEQ ID:1), a 36-amino acid synthetic peptide corresponding to amino acids 638 to 673 of the transmembrane protein (TM) gp41 from the HIV-1 isolate LAI, which exhibits potent anti-HIV-1 activity. As evidenced by the example presented below, in Section 6, the DP-178 (SEQ ID:1) anti-viral activity is so high that, on a weight basis, no other known anti-HIV agent is effective at concentrations as low as those at which DP-178 (SEQ ID:1) exhibits its inhibitory effects. The invention further relates to those portions, analogs, and

homologs of DP-178 which also show such antiviral activity. The antiviral activity of such DP-178 portions, analogs, and homologs, includes, but is not limited to the inhibition of HIV transmission to uninfected CD-4<sup>+</sup> cells. The invention relates to the use of DP-178 (SEQ ID:1) and DP-178 fragments and/or analogs or homologs. Such uses may include, but are not limited to, the use of the peptides as inhibitors of human and non-human retroviral, especially HIV, transmission to uninfected cells, and as type and/or subtype-specific diagnostic tools.

An embodiment of the invention is demonstrated below wherein an extremely low concentration of DP-178 (SEQ ID:1), and very low concentrations of a DP-178 homolog (SEQ ID:3) are shown to be potent inhibitors of HIV-1 mediated CD-4<sup>+</sup> cell-cell fusion (i.e., syncytial formation) and infection of CD-4<sup>+</sup> cells by cell-free virus. Further, it is shown that DP-178 (SEQ ID:1) is not toxic to cells, even at concentrations 3 logs higher than the inhibitory DP-178 (SEQ ID:1) concentration.

The invention also relates to analogous DP178 peptides in other enveloped viruses that demonstrate similar antiviral properties.

The invention further relates to peptides analogous to DP-107, a peptide corresponding to amino acids 558-595 of the HIV-1<sub>LAI</sub> transmembrane protein (TM) of gp41, that are present in other enveloped viruses, and demonstrate antiviral properties. The present invention is based, in part, on the surprising discovery that the DP-107 and DP-108 domains of the gp41 protein non-covalently complex with each other, and that their interaction is necessary for the normal activity of the virus. The invention, therefore, further relates to methods for identifying antiviral

compounds that disrupt the interaction between DP-107 and DP-178, and/or between DP-107-like and DP-178-like peptides.

Embodiments of the invention are demonstrated, below, wherein peptides having structural and/or  
5 similarity to DP-107 and DP-178 are identified.

### 3.1. DEFINITIONS

Peptides are defined herein as organic compounds comprising two or more amino acids covalently joined  
10 by peptide bonds. Peptides may be referred to with respect to the number of constituent amino acids, i.e., a dipeptide contains two amino acid residues, a tripeptide contains three, etc. Peptides containing  
15 ten or fewer amino acids may be referred to as oligopeptides, while those with more than ten amino acid residues are polypeptides.

Peptide sequences defined herein are represented by one-letter symbols for amino acid residues as follows:

20 A (alanine)  
R (arginine)  
N (asparagine)  
D (aspartic acid)  
C (cysteine)  
25 Q (glutamine)  
E (glutamic acid)  
G (glycine)  
H (histidine)  
I (isoleucine)  
30 L (leucine)  
K (lysine)  
M (methionine)  
F (phenylalanine)  
P (proline)  
35

S (serine)  
T (threonine)  
W (tryptophan)  
Y (tyrosine)  
V (valine)

5

#### 4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Amino acid sequence of DP-178 (SEQ ID:1) derived from HIV<sub>LAI</sub>; DP-178 homologs derived from HIV-1<sub>SF2</sub> (DP-185; SEQ ID:3), HIV-1<sub>RF</sub> (SEQ ID:4), and  
10 HIV-1<sub>MN</sub> (SEQ ID:5); DP-178 homologs derived from amino acid sequences of two prototypic HIV-2 isolates, namely, HIV-2<sub>rod</sub> (SEQ ID:6) and HIV-2<sub>NIH2</sub> (SEQ ID:7); control peptides: DP-180 (SEQ ID:2), a peptide  
15 incorporating the amino acid residues of DP-178 in a scrambled sequence; DP-118 (SEQ ID:10) unrelated to DP-178, which inhibits HIV-1 cell free virus infection; DP-125 (SEQ ID:8), unrelated to DP-178, was  
also previously shown to inhibit HIV-1 cell free virus infection (Wild et al., 1992, Proc. Natl. Acad. Sci  
20 USA 89:10,537-10,541); DP-116 (SEQ ID:9), unrelated to DP-178 had previously been shown to be negative for inhibition of HIV-1 infection using the cell-free  
virus infection assay (Wild, et al., 1992, Proc. Natl. Acad. Sci USA 89:10,537-10,541). Throughout the  
25 figures, the one letter amino acid code is used.

FIG. 2. Inhibition of HIV-1 cell-free virus infection by synthetic peptides. IC50 refers to the concentration of peptide that inhibits RT production from infected cells by 50% compared to the untreated  
30 control. Control: the level of RT produced by untreated cell cultures infected with the same level of virus as treated cultures.

FIG. 3. Inhibition of HIV-1 and HIV-2 cell-free virus infection by the synthetic peptide DP-178 (SEQ  
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ID:1). IC50: concentration of peptide that inhibits RT production by 50% compared to the untreated control. Control: Level of RT produced by untreated cell cultures infected with the same level of virus as treated cultures.

5       FIG. 4A. Fusion Inhibition Assay. DP-178 (SEQ ID:1) inhibition of HIV-1 prototypic isolate-mediated syncytia formation. Data represents the number of virus-induced syncytia per cell.

10       FIG. 4B. Fusion Inhibition Assay. DP-180 (SEQ ID:2): scrambled control peptide. DP-185 (SEQ ID:3): DP-178 homolog derived from HIV-1<sub>SF2</sub> isolate. Control: number of syncytia produced in the absence of peptide.

15       FIG. 5. Fusion inhibition assay: HIV-1 vs. HIV-2. Data represents the number of virus-induced syncytia per well. ND: not done.

      FIG. 6. Cytotoxicity study of DP-178 (SEQ ID:1) and DP-116 (SEQ ID:9) on CEM cells. Cell proliferation data is shown.

20       FIG. 7. Schematic representation of HIV-gp41 and maltose binding protein (MBP)-gp41 fusion proteins. DP107 and DP178 are synthetic peptides based on the two putative helices of gp41. The letter P in the DP107 boxes denotes an Ile to Pro mutation at amino acid number 578. Amino acid residues are  
25       numbered according to Meyers et al., Human Retroviruses and AIDS, 1991, Theoret. Biol. and Biophys. Group, Los Alamos Natl. Lab., Los Alamos, NM.

      FIG. 8. A point mutation alters the conformation and anti-HIV activity of M41.

30       FIG. 9. Abrogation of DP178 anti-HIV activity. Cell fusion assays were carried out in the presence of 10 nM DP178 and various concentrations of M41Δ178 or M41PA178.

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FIG. 10. Binding of DP178 to leucine zipper of gp41 analyzed by ELISA.

FIG. 11A-B. Models for a structural transition in the HIV-1 TM protein. Two models are proposed which indicate a structural transition from a native oligomer to a fusogenic state following a trigger event (possibly gp120 binding to CD4). Common features of both models include (1) the native state is held together by noncovalent protein-protein interactions to form the heterodimer of gp120/41 and other interactions, principally through gp41 interactive sites, to form homo-oligomers on the virus surface of the gp120/41 complexes; (2) shielding of the hydrophobic fusogenic peptide at the N-terminus (F) in the native state; and (3) the leucine zipper domain (DP107) exists as a homo-oligomer coiled coil only in the fusogenic state. The major differences in the two models include the structural state (native or fusogenic) in which the DP107 and DP178 domains are complexed to each other. In the first model (A; FIG. 11A) this interaction occurs in the native state and in B during the fusogenic state. When triggered, the fusion complex in the model depicted in (A) is generated through formation of coiled-coil interactions in homologous DP107 domains resulting in an extended  $\alpha$ -helix. This conformational change positions the fusion peptide for interaction with the cell membrane. In the second model (B; FIG. 11B), the fusogenic complex is stabilized by the association of the DP178 domain with the DP107 coiled-coil.

FIG. 12. Motif design using heptad repeat positioning of amino acids of known coiled-coils.

FIG. 13. Motif design using proposed heptad repeat positioning of amino acids of DP-107 and DP-178.



FIG. 14. Hybrid motif design crossing GCN4 and DP-107.

FIG. 15. Hybrid motif design crossing GCN4 and DP-178.

5 FIG. 16. Hybrid motif design 107x178x4, crossing DP-107 and DP-178. This motif was found to be the most consistent at identifying relevant DP-107-like and DP-178-like peptide regions.

FIG. 17. Hybrid motif design ALLMOTI5, crossing GCN4, DP-107, and DP-178.

10 FIG. 18. Hybrid motif design crossing GCN4, DP-107, DP-178, c-Fos c-Jun, c-Myc, and Flu Loop 36.

FIG. 19. Motifs designed to identify N-terminal proline-leucine zipper motifs.

15 FIG. 20. Search results for HIV-1 (BRU isolate) envelope protein gp41. Sequence search motif designations: Spades (♠): 107x178x4; Hearts (♥) ALLMOTI5; Clubs (♣): PLZIP; Diamonds (♦): transmembrane region (the putative transmembrane domains were identified using a PC/Gene program  
20 designed to search for such peptide regions). Asterisk (\*): Lupas method. The amino acid sequences identified by each motif are bracketed by the respective characters. Representative sequences chosen based on all searches are underlined and in  
25 bold. DP-107 and DP-178 sequences are marked, and additionally double-underlined and italicized.

FIG. 21. Search results for human respiratory syncytial virus (RSV) strain A2 fusion glycoprotein F1. Sequence search motif designations  
30 are as in FIG. 20.

FIG. 22. Search results for simian immunodeficiency virus (SIV) envelope protein gp41 (AGM3 isolate). Sequence search motif designations  
35 are as in FIG. 20.

FIG. 23. Search results for canine distemper virus (strain Onderstepoort) fusion glycoprotein 1. Sequence search motif designations are as in FIG. 20.

5 FIG. 24. Search results for newcastle disease virus (strain Australia-Victoria/32) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

10 FIG. 25. Search results for human parainfluenza 3 virus (strain NIH 47885) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

FIG. 26. Search results for influenza A virus (strain A/AICHI/2/68) hemagglutinin precursor HA2. Sequence search designations are as in FIG. 20.

15 FIG. 27. Coiled-coil structural similarity and anti-RSV antiviral activity of 35-mer peptides synthesized utilizing the sequence of a 48-amino acid RSV F2 peptide which spans sequences identified utilizing the computer-assisted searches described  
20 herein. For the exact location and motifs utilized, see FIG. 21. "+" symbols are relative indicators of either structural similarity or antiviral activity, with a greater number of "+" symbols indicating a higher relative similarity or antiviral activity.

25 FIG. 28. Coiled-coil structural similarity and anti-RSV antiviral activity of 35-mer peptides synthesized utilizing the sequence of a 53-amino acid RSV F1 peptide which spans sequences identified utilizing the computer-assisted searches described  
30 herein. See FIG. 21 for the exact location and motifs used. "+" symbols are as described for FIG. 27.

FIG. 29. Coiled-coil structural similarity and anti-human parainfluenza 3 virus (HPF3) antiviral activity of 35-mer peptides synthesized utilizing the

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sequence of a 56-amino acid HPF3 peptide which spans sequences identified utilizing computer-assisted searches described herein. For the exact location and motifs utilized, see FIG. 25. "+" symbols are as described in FIG. 27.

5                   FIG. 30. Coiled-coil structural similarity and anti-HPF3 antiviral activity of 35-mer peptides synthesized utilizing the sequence of a 70-amino acid HPF3 peptide which spans sequences identified  
10                   utilizing the computer-assisted searches described herein. For the exact location and motifs utilized, see FIG. 25. "+" symbols are as described in FIG. 27.

#### 5.    DETAILED DESCRIPTION OF THE INVENTION

15                   Described herein are peptides that exhibit potent antiviral activity. These peptides include DP-178 (SEQ ID:1), a gp41-derived 36 amino acid peptide, fragments and/or analogs of DP-178, and peptides which are homologous to DP-178. In addition, these peptides may include peptides exhibiting anti-viral activity  
20                   which are analogous to DP-107, a 38 amino acid peptide corresponding to residues 558 to 595 of the HIV-1<sub>LAI</sub> transmembrane (TM) gp41 protein, and which are present in other enveloped viral proteins. Also described here are assays for testing the antiviral activities  
25                   of such peptides. The present invention is based, in part, of the surprising discovery that the DP-107 and DP-178 domains of the gp41 protein complex with each other via non-covalent protein-protein interactions which are necessary for normal activity of the virus.  
30                   As such, methods are described for the identification of antiviral compounds that disrupt the interaction between DP-107 and DP-178 peptides, and between DP-107-like and DP-178-like peptides. Finally, the use of the peptides of the invention as inhibitors of non-  
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human and human viral and retroviral, especially HIV, transmission are detailed, as is the use of the peptides as diagnostic indicators of the presence of specific, viruses, especially retroviruses.

5 While not limited to any theory of operation, the following model is proposed to explain the potent anti-HIV activity of DP178, based, in part, on the experiments described in the working examples, infra. In the viral protein, gp41, DP178 corresponds to a putative  $\alpha$ -helix region located in the C-terminal end  
10 of the gp41 ectodomain, and appears to associate with a distal site on gp41 whose interactive structure is influenced by the leucine zipper motif, a coiled-coil structure, referred to as DP107. The association of these two domains may reflect a molecular linkage or  
15 "molecular clasp" intimately involved in the fusion process. It is of interest that mutations in the C-terminal  $\alpha$ -helix motif of gp41 (i.e., the D178 domain) tend to enhance the fusion ability of gp41, whereas mutations in the leucine zipper region (i.e.,  
20 the DP107 domain) decrease or abolish the fusion ability of the viral protein. It may be that the leucine zipper motif is involved in membrane fusion while the C-terminal  $\alpha$ -helix motif serves as a molecular safety to regulate the availability of the  
25 leucine zipper during virus-induced membrane fusion.

On the basis of the foregoing, two models are proposed of gp41-mediated membrane fusion which are schematically shown in FIG. 11A-B. The reason for  
30 proposing two models is that the temporal nature of the interaction between the regions defined by DP107 and DP178 cannot, as yet, be pinpointed. Each model envisions two conformations for gp41 - one in a "native" state as it might be found on a resting virion. The other in a "fusogenic" state to reflect  
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conformational changes triggered following binding of gp120 to CD4 and just prior to fusion with the target cell membrane. The strong binding affinity between gp120 and CD4 may actually represent the trigger for the fusion process obviating the need for a pH change such as occurs for viruses that fuse within intracellular vesicles. The two major features of both models are: (1) the leucine zipper sequences (DP107) in each chain of oligomeric envelope are held apart in the native state and are only allowed access to one another in the fusogenic state so as to form the extremely stable coiled-coils, and (2) association of the DP178 and DP107 sites as they exist in gp41 occur either in the native or fusogenic state. FIG. 11A depicts DP178/DP107 interaction in the native state as a molecular class. On the other hand, if one assumes that the most stable form of the envelope occurs in the fusogenic state, the model in FIG. 11B can be considered.

When synthesized as peptides, both DP107 and DP178 are potent inhibitors of HIV infection and fusion, probably by virtue of their ability to form complexes with viral gp41 and interfere with its fusogenic process; e.g., during the structural transition of the viral protein from the native structure to the fusogenic state, the DP178 and DP107 peptides may gain access to their respective binding sites on the viral gp41, and exert a disruptive influence. DP107 peptides which demonstrate anti-HIV activity are described in Applicants' co-pending application Serial No. 07/927,532, filed August 7, 1992, which is incorporated by reference herein in its entirety.

As shown in the working examples, infra, a truncated recombinant gp41 protein corresponding the

ectodomain of gp41 containing both DP107 and DP178 domains (excluding the fusion peptide, transmembrane region and cytoplasmic domain of gp41) did not inhibit HIV-1 induced fusion. However, when a single mutation was introduced to disrupt the coiled-coil structure of the DP107 domain -- a mutation which results in a total loss of biological activity of DP107 peptides -- the inactive recombinant protein was transformed to an active inhibitor of HIV-1 induced fusion. This transformation may result from liberation of the potent DP178 domain from a molecular clasp with the leucine zipper, DP107 domain.

For clarity of discussion, the invention will be described for DP178 peptide inhibitors of HIV. However, the principles may be analogously applied to other fusogenic enveloped viruses, including but not limited to those viruses containing the peptides listed in Tables V through X, below.

#### 5.1. DP-178 AND DP-178-LIKE PEPTIDES

The peptide DP-178 (SEQ ID:1) of the invention corresponds to amino acid residues 638 to 673 of the transmembrane protein gp41 from the HIV-1<sub>LAI</sub> isolate, and has the 36 amino acid sequence (reading from amino to carboxy terminus):

NH<sub>2</sub>-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:1)

In addition to the full-length DP-178 (SEQ ID:1) 36-mer, the peptides of the invention may include truncations of the DP-178 (SEQ ID:1) peptide which exhibit antiviral activity. Such truncated DP-178 (SEQ ID:1) peptides may comprise peptides of between 3 and 36 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 36-mer polypeptide), and

may include but are not limited to those listed in Tables I and II, below. Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group ( $-\text{NH}_2$ ) and "Z" may represent a carboxyl ( $-\text{COOH}$ ) group.

5 Alternatively, as described below, "X" and/or "Z" may represent a hydrophobic group, an acetyl group, a Fmoc group, an amido group, or a covalently attached macromolecule.

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TABLE I  
DP-178 (SEQ ID:1) CARBOXY TRUNCATIONS

X-YTS-Z  
 X-YTSL-Z  
 X-YTSLI-Z  
 X-YTSLIH-Z  
 5 X-YTSLIHS-Z  
 X-YTSLIHSL-Z  
 X-YTSLIHSLI-Z  
 X-YTSLIHSLIE-Z  
 X-YTSLIHSLIEE-Z  
 X-YTSLIHSLIEES-Z  
 X-YTSLIHSLIEESQ-Z  
 10 X-YTSLIHSLIEESQN-Z  
 X-YTSLIHSLIEESQNNQ-Z  
 X-YTSLIHSLIEESQNNQQ-Z  
 X-YTSLIHSLIEESQNNQQE-Z  
 X-YTSLIHSLIEESQNNQQEK-Z  
 X-YTSLIHSLIEESQNNQQEKN-Z  
 X-YTSLIHSLIEESQNNQQEKNE-Z  
 X-YTSLIHSLIEESQNNQQEKNEQ-Z  
 15 X-YTSLIHSLIEESQNNQQEKNEQE-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEEL-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELL-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLE-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELD-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELDK-Z  
 20 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKW-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKWA-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKWAS-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKWASLW-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKWASLWN-Z  
 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKWASLWNW-Z  
 25 X-YTSLIHSLIEESQNNQQEKNEQEELLELDKWASLWNWF-Z

The one letter amino acid code is used.

Additionally,

"X" may represent an amino group, a hydrophobic group,  
 including but not limited to carbobenzoxyl, dansyl, or  
 30 T-butyloxycarbonyl; an acetyl group; a 9-  
 fluorenylmethoxy-carbonyl (Fmoc) group; a  
 macromolecular carrier group including but not limited  
 to lipid-fatty acid conjugates, polyethylene glycol,  
 or carbohydrates.

"Z" may represent a carboxyl group; an amido group; a  
 T-butyloxycarbonyl group; a macromolecular carrier  
 35 group including but not limited to lipid-fatty acid  
 conjugates, polyethylene glycol, or carbohydrates.



TABLE II  
DP-178 (SEQ ID:1) AMINO TRUNCATIONS

	X-NWF-Z
	X-WNWF-Z
	X-LWNWF-Z
5	X-SLWNWF-Z
	X-ASLWNWF-Z
	X-WASLWNWF-Z
	X-KWASLWNWF-Z
	X-DKWASLWNWF-Z
	X-LDKWASLWNWF-Z
	X-ELDKWASLWNWF-Z
	X-LELDKWASLWNWF-Z
10	X-LLELDKWASLWNWF-Z
	X-ELLELDKWASLWNWF-Z
	X-QELLELDKWASLWNWF-Z
	X-EQELLELDKWASLWNWF-Z
	X-NEQELLELDKWASLWNWF-Z
	X-KNEQELLELDKWASLWNWF-Z
	X-EKNEQELLELDKWASLWNWF-Z
	X-QEKNEQELLELDKWASLWNWF-Z
15	X-QQEKNEQELLELDKWASLWNWF-Z
	X-NQQEKNEQELLELDKWASLWNWF-Z
	X-QNQQEKNEQELLELDKWASLWNWF-Z
	X-SQNQQEKNEQELLELDKWASLWNWF-Z
	X-ESQNQQEKNEQELLELDKWASLWNWF-Z
	X-EESQNQQEKNEQELLELDKWASLWNWF-Z
	X-LIEESQNQQEKNEQELLELDKWASLWNWF-Z
20	X-SLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-HSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-IHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z

25     The one letter amino acid code is used.

Additionally,

30     "X" may represent an amino group, a hydrophobic group, including but not limited to carbobenzoxy, dansyl, or T-butyloxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

35     "Z" may represent a carboxyl group; an amido group; a T-butyloxycarbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

The antiviral peptides of the invention also include analogs of DP-178 and/or DP-178 truncations which may include, but are not limited to, peptides comprising the DP-178 (SEQ ID:1) sequence, or DP-178 truncated sequence, containing one or more amino acid  
5 substitutions, insertions and/or deletions. Analogs of DP-178 homologs, described below, are also within the scope of the invention. The DP-178 analogs of the invention exhibit antiviral activity, and may, further, possess additional advantageous features,  
10 such as, for example, increased bioavailability, and/or stability, or reduced host immune recognition.

HIV-1 and HIV-2 envelope proteins are structurally distinct, but there exists a striking amino acid conservation within the DP-178-  
15 corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some conservation of structure and/or function. Therefore, one possible class of amino acid substitutions would include those amino acid changes  
20 which are predicted to stabilize the structure of the DP-178 peptides of the invention.

Amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more amino  
25 acids of the DP-178 (SEQ ID:1) peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. When only conserved substitutions are  
30 made, the resulting peptide is functionally equivalent to DP-178 (SEQ ID:1) or the DP-178 peptide from which it is derived. Non-conserved substitutions consist of replacing one or more amino acids of the DP-178 (SEQ ID:1) peptide sequence with amino acids possessing  
35 dissimilar charge, size, and/or hydrophobicity

characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

Amino acid insertions may consist of single amino acid residues or stretches of residues ranging from 2 to 15 amino acids in length. One or more insertions  
5 may be introduced into DP-178 (SEQ ID:1), DP-178 fragments, analogs and/or DP-178 homologs (described below).

Deletions of DP-178 (SEQ ID:1), DP-178 fragments, analogs, and/or DP-178 homologs (described below) are  
10 also within the scope of the invention. Such deletions consist of the removal of one or more amino acids from the DP-178 or DP-178-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids. Such deletions may  
15 involve a single contiguous or greater than one discrete portion of the peptide sequences.

The peptides of the invention may further include homologs of DP-178 (SEQ ID:1) and/or DP-178 truncations which exhibit antiviral activity. Such  
20 DP-178 homologs are peptides whose amino acid sequences are comprised of the amino acid sequences of peptide regions of other (*i.e.*, other than HIV-1<sub>LAI</sub>) viruses that correspond to the gp41 peptide region from which DP-178 (SEQ ID:1) was derived. Such  
25 viruses may include, but are not limited to, other HIV-1 isolates and HIV-2 isolates. DP-178 homologs derived from the corresponding gp41 peptide region of other (*i.e.*, non HIV-1<sub>LAI</sub>) HIV-1 isolates may include, for example, peptide sequences as shown below.

30

NH<sub>2</sub>-YTNTIYTLLEESQNQQEKNEQEELLELDKWASLWNWF-COOH (DP-185; SEQ ID:3);

35

NH<sub>2</sub>-YTGIIYNLLEESQNQQEKNEQEELLELDKWANLWNWF-COOH (SEQ ID:4);

NH<sub>2</sub>-YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:5).

SEQ ID:3 (DP-185), SEQ ID:4, and SEQ ID:5 are derived from HIV-1<sub>SF2</sub>, HIV-1<sub>RF</sub>, and HIV-1<sub>MN</sub> isolates, respectively. Underlined amino acid residues refer to those residues that differ from the corresponding position in the DP-178 (SEQ ID:1) peptide. One such DP-178 homolog, DP-185 (SEQ ID:3), is described in the Working Example presented in Section 6, below, where it is demonstrated that DP-185 (SEQ ID:3) exhibits antiviral activity. The DP-178 homologs of the invention may also include truncations, amino acid substitutions, insertions, and/or deletions, as described above.

In addition, striking similarities, as shown in FIG. 1, exist within the regions of HIV-1 and HIV-2 isolates which correspond to the DP-178 sequence. A DP-178 homolog derived from the HIV-2<sub>NIHZ</sub> isolate has the 36 amino acid sequence (reading from amino to carboxy terminus):

NH<sub>2</sub>-LEANISQSLEQAQIQQEKNMVELQKLNSWDVFTNWL-COOH (SEQ ID:7)

Table III and Table IV show some possible truncations of the HIV-2<sub>NIHZ</sub> DP-178 homolog, which may comprise peptides of between 3 and 36 amino acid residues (*i.e.*, peptides ranging in size from a tripeptide to a 36-mer polypeptide). Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group (-NH<sub>2</sub>) and "Z" may represent a carboxyl (-COOH) group. Alternatively, as described below, "X" and/or "Z" may represent a hydrophobic group, an acetyl group, a FMOC group, an amido group, or a covalently attached macromolecule, as described below.

TABLE III

HIV-2<sub>NH2</sub> DP-178 homolog carboxy truncations.

	X-LEA-Z
	X-LEAN-Z
	X-LEANI-Z
	X-LEANIS-Z
5	X-LEANISQ-Z
	X-LEANISQS-Z
	X-LEANISQSL-Z
	X-LEANISQSLE-Z
	X-LEANISQSLEQ-Z
	X-LEANISQSLEQA-Z
	X-LEANISQSLEQAQ-Z
10	X-LEANISQSLEQAQI-Z
	X-LEANISQSLEQAQIQ-Z
	X-LEANISQSLEQAQIQQ-Z
	X-LEANISQSLEQAQIQQE-Z
	X-LEANISQSLEQAQIQQEK-Z
	X-LEANISQSLEQAQIQQEKN-Z
	X-LEANISQSLEQAQIQQEKNM-Z
	X-LEANISQSLEQAQIQQEKNMY-Z
15	X-LEANISQSLEQAQIQQEKNMYE-Z
	X-LEANISQSLEQAQIQQEKNMYEL-Z
	X-LEANISQSLEQAQIQQEKNMYELQ-Z
	X-LEANISQSLEQAQIQQEKNMYELQK-Z
	X-LEANISQSLEQAQIQQEKNMYELQKL-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLN-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNS-Z
20	X-LEANISQSLEQAQIQQEKNMYELQKLNSW-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWD-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDV-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVF-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFT-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW-Z
	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z

25 The one letter amino acid code is used.

Additionally,

30 "X" may represent an amino group, a hydrophobic group, including but not limited to carbobenzoxyl, dansyl, or T-butyloxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (Fmoc) group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

35 "Z" may represent a carboxyl group; an amido group; a T-butyloxycarbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

TABLE IV

HIV-2<sub>NIH</sub> DP-178 homolog amino truncations.

	X-NWL-Z
	X-TNWL-Z
	X-FTNWL-Z
5	X-VFTNWL-Z
	X-DVFTNWL-Z
	X-WDVFTNWL-Z
	X-SWDVFTNWL-Z
	X-NSWDVFTNWL-Z
	X-LNSWDVFTNWL-Z
	X-KLNSWDVFTNWL-Z
	X-QKLNSWDVFTNWL-Z
10	X-LQKLNSWDVFTNWL-Z
	X-ELQKLNSWDVFTNWL-Z
	X-YELQKLNSWDVFTNWL-Z
	X-MYELQKLNSWDVFTNWL-Z
	X-NMYELQKLNSWDVFTNWL-Z
	X-KNMYELQKLNSWDVFTNWL-Z
	X-EKNMYELQKLNSWDVFTNWL-Z
	X-QEKNMYELQKLNSWDVFTNWL-Z
15	X-QQEKNMYELQKLNSWDVFTNWL-Z
	X-IQQEKNMYELQKLNSWDVFTNWL-Z
	X-QIQQEKNMYELQKLNSWDVFTNWL-Z
	X-AQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-QAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-EAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-LEAQIQQEKNMYELQKLNSWDVFTNWL-Z
20	X-SLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-QSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-SQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-ISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-NISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-ANISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-EANISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
25	X-LEANISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z

The one letter amino acid code is used.

Additionally,

"X" may represent an amino group, a hydrophobic group, including but not limited to carbobenzoxyl, dansyl, or T-butyloxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (Fmoc) group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

"Z" may represent a carboxyl group; an amido group; a T-butyloxycarbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

## 5.2. DP-107 and DP-178 ANALOGOUS ANTIVIRAL PEPTIDES

Peptide sequences functionally corresponding, and thus analogous to, the DP-178 sequences of the invention, described, above, in Section 5.1 may be found in other, non-HIV-1 envelope viruses. Further, peptide sequences functionally corresponding, and thus analogous to, DP-107, an HIV-1-derived antiviral peptide, may also be found in other, non-HIV-1 envelope viruses. DP-107 is a 38 amino acid peptide corresponding to residues 558 to 595 of HIV-1<sub>LAI</sub> transmembrane (TM) gp41 protein, which exhibits potent anti-viral activity. DP-107 is more fully described in Applicant's co-pending U.S. Patent Application Ser. No. 07/927,532. These DP-107-like and DP-178-like analogous peptides and present in TM proteins of envelope viruses and preferably exhibit antiviral activity, most preferably antiviral activity which is specific to the virus in which their native sequences are found.

DP-107-like and DP-178-like peptides may be identified, for example, by utilizing a computer-assisted search strategy such as that described and demonstrated, below, in the Examples presented in Sections 9 through 16. The search strategy identifies regions in other viruses that are similar in predicted secondary structure to DP-107 and DP-178.

This search strategy is described fully, below, in the Example presented in Section 9. While this search strategy is based, in part, on a primary amino acid motif deduced from DP-107 and DP-178, it is not based solely on searching for primary amino acid sequence homologies, as such protein sequence homologies exist within, but not between major groups of viruses. For example, primary amino acid sequence homology is high within the TM protein of different

strains of HIV-1 or within the TM protein of different isolates of simian immunodeficiency virus (SIV).

Primary amino acid sequence homology between HIV-1 and SIV, however, is low enough so as not to be useful.

5 It is not possible, therefore, to find DP-107 or DP-178-like peptides within other viruses, whether structurally, or otherwise, based on primary sequence homology, alone.

Further, while it would be potentially useful to identify primary sequence arrangements of amino acids  
10 based on the physical chemical characteristics of different classes of amino acids rather than based on the specific amino acids themselves, for instance, a by concentrating on the coiled-coil nature of the peptide sequence, a computer algorithm designed by  
15 Lupas et al. to identify such coiled-coil propensities of regions within proteins (Lupas, A., et al., 1991 Science 252:1162-1164) is inadequate for identifying protein regions analogous to DP-107 or DP-178.

Specifically, analysis of HIV-1 gp160 (containing  
20 both gp120 and gp41) using the Lupas algorithm does not identify the coiled-coil region within DP-107. It does, however, identify a region within DP-178 beginning eight amino acids N-terminal to the start of DP-178 and ending eight amino acids from the C-  
25 terminus. The DP-107 peptide has been shown experimentally to form a stable coiled coil. A search based on the Lupas search algorithm, therefore, would not have identified the DP-107 coiled-coil region. Conversely, the Lupas algorithm identified the DP-178  
30 region as a potential coiled-coil motif. However, the peptide DP-178 derived from this region failed to form a coiled coil in solution. A possible explanation for the inability of the Lupas search algorithm to accurately identify coiled-coil sequences within the  
35 HIV-1 TM, is that the Lupas algorithm is based on the



structure of coiled coils from proteins that are not structurally or functionally similar to the TM proteins of viruses, antiviral peptides (e.g. DP-107 and DP-178) of which are an object of this invention.

5       The computer search strategy of the invention, as demonstrated in the Examples presented below, in Sections 9 through 16, successfully identifies regions of viral TM proteins similar to DP-107 or DP-178. This search strategy was designed to be used with a commercially-available sequence database packages,  
10       preferably PC/Gene. A series of motifs were designed and engineered to range in stringency from very strict to very broad, as discussed in Section 9.

      Among the protein sequence search motifs which may be utilized in such a computer-assisted DP-107-like  
15       and DP-178-like antiviral peptide search are the 107x178x4 motif, the ALLMOTI5 motif, and the PLZIP series of motifs, each of which is described in the Example presented in Section 9, below, with 107x178x4 being preferred.

20       Coiled-coiled sequences are thought to consist of heptad amino acid repeats. For ease of description, the amino acid positions within the heptad repeats are sometimes referred to as A through G, with the first position being A, the second B, etc. The motifs used  
25       to identify DP-107-like and DP-178-like sequences herein are desined to specifically search for and identify such heptad repeats. In the descriptions of each of the motifs described, below, amino acids enclosed by brackets , i.e., [], designate the only  
30       amino acid residues that are acceptable at the given position, while amino acids enclosed by braces, i.e., {}, designate the only amino acids which are unacceptable at the given heptad position. When a set of bracketed or braced amino acids is followed by a  
35       number in parentheses i.e., (), it refers to the

number of subsequent amino acid positions for which the designated set of amino acids hold, e.g., a (2) means "for the next two heptad amino acid positions.

The ALLMOTI5 is written as follows:

```

5      {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
      {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
      {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
      {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
      {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-

```

Translating this motif, it would read: "at the first (A) position of the heptad, any amino acid residue except C, D, G, H, or P is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, or P is acceptable, at the fourth heptad position (D), any amino acid residue except C, D, G, H, or P is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, or P is acceptable. This motif is designed to search for five consecutive heptad repeats (thus the repeat of the first line five times), meaning that it searches for 35-mer sized peptides. It may also be designed to search for 28-mers, by only repeating the initial motif four times. With respect to the ALLMOTI5 motif, a 35-mer search is preferred. Those viral sequences identified via such an ALLMOTI5 motif are listed in Table V, below, at the end of this Section. The viral sequences listed in Table V potentially exhibit antiviral activity, may be useful in the the identification of antiviral compounds, and are intended to be within the scope of the invention.

The 107x178x4 motif is written as follows:

```

30  [EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-
    [EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-
    [EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-
    [EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-

```

Translating this motif, it would read: "at the first (A) position of the heptad, any amino acid residue except E, F, I, K, L, N, Q, S, T, V, W, or Y

is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, M or P is acceptable, at the fourth position (D), any amino acid residue except E, F, I, K, L, N, Q, S, T, V, W, or Y is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, M or P is acceptable. This motif is designed to search for four consecutive heptad repeats (thus the repeat of the first line four times), meaning that it searches for 28-mer sized peptides. It may also be designed to search for 35-mers, by repeating the initial motif five times. With respect to the 107x178x4 motif, a 28-mer search is preferred. Those viral sequences identified via such a 107x178x4 motif are listed in Table V, below, at the end of this Section. The viral sequences listed in Table V potentially exhibit antiviral activity, may be useful in the the identification of antiviral compounds, and are intended to be within the scope of the invention.

The PLZIP series of motifs are as listed in FIG. 19. These motifs are designed to identify leucine zipper coiled-coil like heptads wherein at least one proline residue is present at some predefined distance N-terminal to the repeat. These PLZIP motifs find regions of proteins with similarities to HIV-1 DP-178 generally located just N-terminal to the transmembrane anchor. These motifs may be translated according to the same convention described above. Each line depicted in FIG. 19 represents a single, complete search motif. "X" in these motifs refers to any amino acid residue. In instances wherein a motif contains two numbers within parentheses, this refers to a variable number of amino acid residues. For example, X (1,12) is translated to "the next one to twelve amino acid residues, inclusive, may be any amino acid".

Tables VI through X, below, at the end of this

Section, list hits from such PLZIP motifs. The viral sequences listed in Table VI through X potentially exhibit antiviral activity, may be useful in the the identification of antiviral compounds, and are intended to be within the scope of the invention.

5       The Examples presented in Sections 17 and 18, below, demonstrate that respiratory syncytial virus and parainfluenza virus sequences identified via such a computer search exhibit antiviral and/or structural characteristics similar to those of DP-107 or DP-178.

10       The DP-107-like and DP-178-like analogous peptides may, further, contain any of the additional groups described for DP-178, above, in Section 5.1. For example, these peptides may include any of the additional amino-terminal groups which "X" of Tables I  
15 through IV may represent, and may also include any of the carboxy-terminal groups which "Z" of Tables I through IV may represent.

      Additionally, such DP-107-like and DP-178-like peptides may furthr include DP-107-like or DP-178-like  
20 peptides, such as those listed in Tables V through X, above, containing one or more amino acid substitutions, insertions, and/or deletions. Also, analogs of such DP-107-like and DP-178-like peptides are intended to be within the scope of the invention.  
25 Such analogs of the invention may exhibit increased antiviral activity, and may, further, posses increased bioavailability, and/or stability, or reduced immune recognition.

      The DP-107-like and DP-178-like amino acid  
30 substitutions, insertions and deletions, are as described for DP-178, above, in Section 5.1. Analog modifications are as described, below, in Section 5.3.

35

**TABLE V**

Search Results Summary for 107x178x4 and  
ALLMOTI5 Motifs

[illegible]

PENV HV1H3	545-594	631-593	791-818		PENV HV1BN	501-590	608-708	793-831		
PENV HV1J3	558-595	642-594	802-829		PENV HV1BR	510-599	615-717	772-841		
PENV HV1JR		622-675	783-811		PENV HV1C4	510-606	626-724	779-855		
PENV HV1KB	555-596	637-677	776-824		PENV HV1EL	502-581	607-709	768-829		
PENV HV1MA	547-595	633-707	794-826		PENV HV1H2	505-594	610-712	767-838		
PENV HV1MF	543-592	629-681	789-816		PENV HV1H3	505-594	610-712	767-843		
PENV HV1MN	567-595	632-684	791-819		PENV HV1J3	517-605	622-723	778-843		
PENV HV1ND	535-593	621-673	783-813		PENV HV1JR	487-588	603-704	769-835		
PENV HV1OY	544-593	630-704	789-820		PENV HV1KB	511-545	555-599	618-718	772-848	
PENV HV1PV	545-594	631-683	791-818		PENV HV1MA	507-596	617-714	770-825		
PENV HV1RH	554-602	640-692	800-832		PENV HV1MF	503-592	622-710	765-841		
PENV HV1S1	536-595	622-674	782-808		PENV HV1MN	508-595	617-713	774-841		
PENV HV1S3	541-599	627-679	787-815		PENV HV1ND	495-584	601-702	757-825		
PENV HV1SC	545-593	631-683	791-818		PENV HV1OY	487-583	610-711	766-842		
PENV HV1W1	545-593	631-683	791-818		PENV HV1PV	505-594	610-712	767-843		
PENV HV1W2	538-584	622-674	782-808		PENV HV1RH	507-603	618-721	776-852		
PENV HV1Z2	542-591	628-680	790-820		PENV HV1S1	498-585	602-703	768-830		
PENV HV1Z6	545-593	630-682	792-822		PENV HV1S3	494-580	607-708	763-837		
PENV HV1Z8	573-601	634-678	797-828		PENV HV1SC	488-584	611-712	767-834		
PENV HV1ZH	545-594	627-686	791-823		PENV HV1W1	488-584	611-712	767-838		
PENV HV2BE	532-591	621-648	653-697		PENV HV1W2	488-584	602-703	758-827		
PENV HV2CA	534-593	623-650	655-698		PENV HV1Z2	502-591	607-709	764-831		
PENV HV2D1	523-550	555-582	644-688		PENV HV1Z6	504-593	608-711	766-840		
PENV HV2G1	524-551	558-583	613-840	645-693	PENV HV1Z8	512-601	617-675	682-719	774-831	
PENV HV2NZ	524-551	558-583	613-840	662-699	PENV HV1ZH	522-594	612-712	777-839		
PENV HV2RO	533-592	622-688			PENV HV2BE	510-595	617-680			
PENV HV2S2	527-554	550-586	648-692		PENV HV2CA	512-597	619-709			
PENV HV2S8	557-594	614-673			PENV HV2D1	501-588	608-688			
PENV HV2S1	527-554	550-586	648-692		PENV HV2G1	502-597	609-689			
PENV MCFF	473-512				PENV HV2NZ	488-587	608-688			
PENV MCFF3	488-515				PENV HV2RO	511-590	616-708			
PENV MLVAV	517-544				PENV HV2S2	505-590	612-702			
PENV MLVCB	510-539				PENV HV2S8	526-588	614-700			
PENV MLVF5	523-553				PENV HV2ST	505-590	612-702			
PENV MLVFF	523-553				PENV IPMAE	307-422	485-527			
PENV MLVFF	523-553				PENV JSRV	403-455	571-605			
PENV MLVHO	510-540				PENV MCFF	473-525	537-571			
PENV MLVK1	40-81				PENV MCFF3	474-528	538-572			
PENV MLVMO	502-543				PENV MLVAV	503-555	567-601			
PENV MLVRD	497-538				PENV MLVCB	498-550	562-596			
PENV MLVRK	497-538				PENV MLVF5	520-584	576-610			
PENV MMTVB	458-485	562-588			PENV MLVFF	520-584	576-610			
PENV MMTVG	458-485	562-588			PENV MLVFP	520-584	576-610			
PENV MPMV	422-470				PENV MLVHO	504-551	563-597			
PENV MSVFB	57-84				PENV MLVK1	40-82	104-138			
PENV OMVVS	42-69	186-223	780-807		PENV MLVMO	502-554	566-600			
PENV RMCV	487-517				PENV MLVRD	497-549	561-595			

PENV SFV1	14-41	888-801				PENV MLVRK	497-549	581-595				
PENV SFV3L	18-45	319-357	673-700	883-898		PENV MMTVB	477-539	556-612				
PENV SIVA1	581-588	592-619	652-679	697-724		PENV MMTVG	477-539	556-612				
PENV SIVAQ	588-593	597-624	658-685	703-730		PENV MPV	408-474					
PENV SIVAI	548-603	634-708				PENV MSVFB	43-95	107-141				
PENV SIVAT	580-617	651-678				PENV OMVVB	22-84	185-223	684-746	780-816		
PENV SIVCZ	526-584	627-654				PENV RMCV	484-528	540-574				
PENV SIVGB	589-650	784-816				PENV RFFV	342-378					
PENV SIVM1	550-609	671-715				PENV SFV1	1-41	101-140	154-205	321-355	593-651	868-804
PENV SIVM2	158-215	277-288				PENV SFV3L	5-46	158-209	318-357	590-708	883-901	
PENV SIVMK	553-608					PENV SIVA1	289-310	551-623	643-683			
PENV SIVML	548-608					PENV SIVAG	558-628	651-698	808-852			
PENV SIVS4	553-612	642-668	691-718			PENV SIVAI	257-291	336-370	535-607	827-840		
PENV SIVSP	554-595	646-722				PENV SIVAT	284-288	549-621	644-692	786-833		
PENV SMRVH	400-462					PENV SIVCZ	253-291	330-365	512-584	699-703	803-837	
PENV SRV1	408-471					PENV SIVGB	588-654	877-725				
PENV VILV	773-800					PENV SIVM1	114-151	485-508	528-613	635-725	808-864	
PENV VILV1	780-807					PENV SIVM2	71-116	134-219	245-331			
PENV VILV2	782-809					PENV SIVMK	484-505	540-612	638-724			
PHEMA CVBLY	208-242					PENV SIVML	484-505	540-612	638-724			
PHEMA CVBM	208-242					PENV SIVS4	468-509	517-616	638-728	812-853		
PHEMA CVBQ	208-242					PENV SIVSP	470-513	521-620	642-732	811-848		
PHEMA CVHOC	208-242					PENV SMRVH	400-468					
PHEMA IAAIC	387-453					PENV SRV1	408-475					
PHEMA IABAN	371-437					PENV VILV	21-62	194-222	637-740	773-809		
PHEMA IABUD	381-451					PENV VILV1	21-62	194-222	643-748	780-816		
PHEMA IACKA	381-451					PENV VILV2	21-62	194-222	645-748	782-818		
PHEMA IACKG	382-441	484-528				PHEMA CVBLY	208-242					
PHEMA IACKP	388-428					PHEMA CVBM	208-242					
PHEMA IACKQ	388-428					PHEMA CVBQ	208-242					
PHEMA IACKV	384-443					PHEMA CVHOC	208-242					
PHEMA IADA1	381-451					PHEMA IAAIC	380-458					
PHEMA IADA2	423-453	489-543				PHEMA IABAN	384-440					
PHEMA IADA3	387-453					PHEMA IABUD	378-454					
PHEMA IADA4	418-478					PHEMA IACKA	378-454					
PHEMA IADCZ	381-451					PHEMA IACKG	108-142	375-475	484-528			
PHEMA IADE1	402-453	508-533				PHEMA IACKP	360-452	487-532				
PHEMA IADH1	371-437					PHEMA IACKQ	360-452	487-532				
PHEMA IADH2	371-437					PHEMA IACKS	377-469	504-549				
PHEMA IADH3	371-437					PHEMA IACKV	112-148	377-489				
PHEMA IADH4	371-437					PHEMA IADA1	377-454					
PHEMA IADH5	371-437					PHEMA IADA2	377-478	495-547				
PHEMA IADH6	371-437					PHEMA IADA3	380-453					
PHEMA IADH7	371-437					PHEMA IADA4	378-478	508-548				
PHEMA IADIR	416-446					PHEMA IADCZ	378-454					
PHEMA IADM2	387-453					PHEMA IADE1	21-55	377-472				
PHEMA IADNZ	381-451					PHEMA IADH1	384-440					



PHEMA_IADU3	387-463						PHEMA_IADH2	384-440					
PHEMA_IAEN7	387-453						PHEMA_IADH3	384-440					
PHEMA_IAPPR	384-442						PHEMA_IADH4	384-440					
PHEMA_IAGRE	381-451						PHEMA_IADH5	384-440					
PHEMA_IAGU2	505-532						PHEMA_IADH6	384-440					
PHEMA_IAGUA	504-531						PHEMA_IADH7	384-440					
PHEMA_Iahal	386-452						PHEMA_IADIR	379-471	508-551				
PHEMA_Iahc8	388-457						PHEMA_IADMI	21-55					
PHEMA_Iahc7	388-457						PHEMA_IADIM2	380-458					
PHEMA_Iahcd	388-457						PHEMA_IADNY	21-55					
PHEMA_Iahde	388-457						PHEMA_IADNZ	378-454					
PHEMA_Iahfo	388-452						PHEMA_IADU1	21-55					
PHEMA_Iahk6	388-452						PHEMA_IADU3	380-458					
PHEMA_Iahk7	388-452						PHEMA_IAEN7	380-458					
PHEMA_Iahle	388-457						PHEMA_IAPPR	377-477					
PHEMA_Iahlo	388-457						PHEMA_IAGRE	378-454					
PHEMA_Iahmi	388-452						PHEMA_IAGU2	378-473					
PHEMA_Iahnm	388-452						PHEMA_IAGUA	377-478					
PHEMA_Iahnn	388-457						PHEMA_Iahal	379-455					
PHEMA_Iahpr	388-457						PHEMA_Iahc8	112-148	380-484	503-537			
PHEMA_Iahro	388-452						PHEMA_Iahc7	112-148	380-484	503-537			
PHEMA_Iahsa	388-452						PHEMA_Iahcd	380-484	503-537				
PHEMA_Iahsp	388-457						PHEMA_Iahde	380-484	503-537				
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PHEMA_Iahte	388-452						PHEMA_Iahk6	378-455					
PHEMA_Iahto	388-456						PHEMA_Iahk7	378-455					
PHEMA_Iahur	388-452						PHEMA_Iahle	112-148	380-484	503-537			
PHEMA_Iakie	425-478						PHEMA_Iahlo	112-148	380-484	503-537			
PHEMA_Ialen	425-478						PHEMA_Iahmi	378-455					
PHEMA_Iamaa	380-450						PHEMA_Iahnm	378-455					
PHEMA_Iamab	385-455						PHEMA_Iahnn	112-148	380-484	503-537			
PHEMA_Iamao	387-453						PHEMA_Iahpr	112-148	380-484	503-537			
PHEMA_Iame1	387-453						PHEMA_Iahro	378-455					
PHEMA_Iame2	387-453						PHEMA_Iahsa	378-455					
PHEMA_Iame6	371-437						PHEMA_Iahsp	112-148	380-484	503-537			
PHEMA_Iamin	382-441						PHEMA_Iahsw	112-148	380-484	503-537			
PHEMA_Iant6	387-453						PHEMA_Iahte	378-455					
PHEMA_Iapil	505-534						PHEMA_Iahto	378-455					
PHEMA_Iapue	425-478						PHEMA_Iahur	378-455					
PHEMA_Iarud	381-451						PHEMA_Iajap	378-457	502-547				
PHEMA_Iase2	381-451						PHEMA_Iakie	378-478	508-541				
PHEMA_Iash2	508-547						PHEMA_Ialen	378-478	508-548				
PHEMA_Iasta	384-443						PHEMA_Iamaa	377-453					
PHEMA_Iatki	415-445						PHEMA_Iamab	382-458					
PHEMA_Iatkm	381-451						PHEMA_Iamao	380-458					
PHEMA_Iatko	507-534						PHEMA_Iame1	380-458					
PHEMA_Iatkp	424-454					493-539	PHEMA_Iame2	380-458					

PHEMA_IATKR	381-422						PHEMA_IAME6	384-440				
PHEMA_IATKW	419-449	500-536					PHEMA_IAMIN	108-142	375-475			
PHEMA_IAUDO	387-453						PHEMA_IANT6	380-456				
PHEMA_IAUSS	425-478						PHEMA_IAPIL	378-477	498-534			
PHEMA_IAVI7	388-454						PHEMA_IAPUE	378-478	508-548			
PHEMA_IAWIL	424-477						PHEMA_IARUD	378-454				
PHEMA_IAZCO	387-453						PHEMA_IASE2	378-454				
PHEMA_IJAZH2	371-437						PHEMA_IASH2	378-474	508-552			
PHEMA_IJZH3	371-437						PHEMA_IASTA	112-148	377-469			
PHEMA_IJAZIN	418-478	508-547					PHEMA_IATKI	378-471	508-551			
PHEMA_IJAZNJ	418-478	508-547					PHEMA_IATKM	378-454				
PHEMA_IJAZUK	387-453						PHEMA_IATKO	392-470	504-548			
PHEMA_INBBE	400-431	439-483					PHEMA_IATKP	378-454	493-540			
PHEMA_INBBO	380-421	429-473					PHEMA_IATKR	30-84	374-474			
PHEMA_INBEN	398-428	437-481					PHEMA_IATKW	373-472	487-539			
PHEMA_INBHK	381-418	428-473					PHEMA_IATRA	21-55				
PHEMA_INBLE	398-430	438-482					PHEMA_IAUDO	387-458				
PHEMA_INBMD	389-420	428-472					PHEMA_IAUSS	376-478	508-548			
PHEMA_INBME	393-424	432-476					PHEMA_IAVI7	381-457				
PHEMA_INBOR	398-429	437-481					PHEMA_IAWIL	375-477	505-547			
PHEMA_INBSI	398-429	437-481					PHEMA_IAZCO	380-456				
PHEMA_INBUS	381-422	430-474					PHEMA_IJZH2	384-440				
PHEMA_INBVI	393-424	432-476					PHEMA_IJZH3	384-440				
PHEMA_INBVK	400-431	439-483					PHEMA_IJAZIN	378-478	508-548			
PHEMA_INCCA	496-571						PHEMA_IJZNJ	378-478	508-548			
PHEMA_INCEN	483-559						PHEMA_IJZUK	380-456				
PHEMA_INCGL	483-559						PHEMA_INBBE	388-473				
PHEMA_INCHY	482-558						PHEMA_INBBO	378-483				
PHEMA_INCJH	498-672						PHEMA_INBEN	388-471				
PHEMA_INCKY	482-558						PHEMA_INBHK	381-463				
PHEMA_INCMI	482-558						PHEMA_INBLE	387-472				
PHEMA_INCNA	482-558						PHEMA_INBMD	377-482				
PHEMA_INCP1	483-559						PHEMA_INBME	381-468				
PHEMA_INCP2	483-559						PHEMA_INBOR	388-471				
PHEMA_INCP3	483-559						PHEMA_INBSI	388-471				
PHEMA_INCTA	483-559						PHEMA_INBUS	378-484				
PHEMA_INCYA	483-559						PHEMA_INBVI	381-468				
PHEMA_NDVA	64-81						PHEMA_INBVK	388-473				
PHEMA_NDV8	64-81						PHEMA_INCCA	483-571				
PHEMA_NDVO	64-81						PHEMA_INCEN	471-559				
PHEMA_NDVH	64-81						PHEMA_INCGL	471-559				
PHEMA_NDVI	64-81						PHEMA_INCHY	470-558				
PHEMA_NDVM	64-81						PHEMA_INCJH	494-572				
PHEMA_NDVQ	64-81						PHEMA_INCKY	470-558				
PHEMA_NDVTG	64-81						PHEMA_INCMI	470-558				
PHEMA_NDVU	64-81						PHEMA_INCNA	470-558				
PHEMA_PHODV	39-68	46-73					PHEMA_INCP1	471-559				

PHEMA PI1HW	78-110	306-393							PHEMA INCP2	471-559			
PHEMA PI3B	88-83								PHEMA INCP3	471-559			
PHEMA PI3H4	27-61								PHEMA INCTA	471-559			
PHEMA PI3HA	27-61								PHEMA INCYA	471-559			
PHEMA PI3HT	27-78								PHEMA MEASE	48-90			
PHEMA PI3HU	23-70								PHEMA MEASH	48-80			
PHEMA PI3HV	27-91								PHEMA MEASI	48-87			
PHEMA PI3HW	27-61								PHEMA MEASY	48-87			
PHEMA PI3HX	27-61								PHEMA MUMPM	34-89			
PHEMA RACVI	188-214	258-283							PHEMA MUMPR	34-89			
PHEMA SEND6	78-106								PHEMA MUMPS	34-89			
PHEMA SENDF	78-106								PHEMA NDVA	8-52	477-529		
PHEMA SENDH	78-106								PHEMA NDVB	1-49			
PHEMA SENDJ	78-106								PHEMA NDVD	1-49			
PHEMA SENDZ	78-106								PHEMA NDVM	1-49			
PHEMA SV41	22-52	394-421							PHEMA NDVO	1-49			
PHEMA VACCC	118-146	175-202	218-243						PHEMA NDVTG	1-49			
PHEMA VACCI	108-148	175-202	218-243						PHEMA NDVU	1-49			
PHEMA VACCT	118-148	175-202	218-243						PHEMA PHODV	39-73			
PHEMA VACCV	108-146	175-202	215-242						PHEMA PI1HW	68-110			
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PVENV EAV	120-147								PHEMA PI2HT	247-281			
PVENV THOGV	313-347								PHEMA PI3B	38-93			
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PVF03 VACCV	71-110	185-212							PHEMA PI3HA	20-110	394-428		
PVF05 VACCP	33-60								PHEMA PI3HT	13-110	394-428		
PVF05 VACCV	33-60								PHEMA PI3HU	13-110	394-428		
PVF11 VACCC	274-321								PHEMA PI3HV	13-110	394-428		
PVF11 VACCP	270-317								PHEMA PI3HW	13-110	394-428		
PVF12 VACCC	10-37	113-140	554-581						PHEMA PI3HX	13-110	394-428		
PVF12 VACCP	10-37	113-140	554-581						PHEMA PI3HA	54-88			
PVF18 VACCC	35-62	152-178							PHEMA RACVI	188-214	256-280		
PVF18 VACCV	35-62	152-178							PHEMA RINDK	48-87			
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PVFUS VACCC	37-84								PHEMA SENDF	57-110			
PVFUS VACCV	37-64								PHEMA SENDH	57-110			
PVG01 VACCC	225-252	301-335							PHEMA SENDJ	57-110			
PVG01 VACCV	184-181	240-274							PHEMA SENDZ	57-110			
PVG01 VARV	225-252	301-335							PHEMA SV41	18-52	387-421		
PVG02 VACCV	96-123								PHEMA SV5	27-82			
PVG02 VARV	98-123								PHEMA SV5LN	27-82			
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PVG03 H9VEK	148-178								PVENV DHV11	318-366			
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PVG05 VARV	48-75	124-161	256-289	355-389					PVENV MCV2	252-286			
PVG07 H8V11	71-88								PVENV THOGV	313-364			

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PVG08 VACCV	271-301						PVENV VACCI	257-285					
PVG08 VARV	308-338						PVENV VACCP	257-285					
PVG12 SPV1R	11-45						PVENV VACCV	257-285					
PVG17 HSV11	177-204						PVF01 VACCC	48-80	124-158				
PVG18 HSV11	174-208						PVF01 VACCV	48-80	124-158				
PVG1 SPV1R	260-287						PVF03 VACCC	71-110					
PVG1 SPV4	287-314	383-410					PVF03 VACCV	71-110					
PVG22 HSV11	373-400	581-622	688-705	768-824			PVF05 VACCC	81-129	282-320				
PVG24 HSV11	31-58						PVF05 VACCP	81-128	282-320				
PVG28 HSV11	253-280						PVF05 VACCV	81-129	283-321				
PVG28 AMEPV	33-84	487-528					PVF11 VACCC	217-258	288-315				
PVG2 SPV1R	285-326	91-118					PVF11 VACCP	213-254	265-311				
PVG2 SPV4	148-173	175-205	282-310				PVF12 VACCC	1-87	102-143	189-236	350-388	544-581	
PVG34 HSV11	95-122						PVF12 VACCP	1-87	102-143	189-236	350-388	544-581	
PVG37 HSV11	442-469						PVF16 VACCC	155-194					
PVG38 HSV11	651-678	1088-1115					PVF16 VACCP	155-194					
PVG3L AMEPV	2-28						PVFP3 FOWPV	1-43					
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PVG3 SPV4	18-52	87-148					PVFP7 FOWPV	23-57					
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PVG48 HSV11	142-169	346-373	887-824	873-1007			PVFUS VACCC	30-84					
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PVG4R AMEPV	4-31						PVG01 BPP22	84-135	400-488	475-513	608-659		
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PVG51 HSV11	34-81	87-114					PVG01 VACCC	301-339					
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PVG83 HSV11	550-584						PVG03 VARV	84-98					
PVG84 HSV11	477-504						PVG05 VACCC	117-158	255-288	355-388			
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PVG88 HSV11	382-408						PVG08 HSV11	81-109					
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PVG75 HSV11	388-422						PVG08 VACCC	304-338					
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PVG12 CVBV	389-426	642-676	1022-1084	1278-1305			PVG1 SPV1R	138-170	258-287	320-357			

[illegible]

PVGLF MEASV	228-282							PVGL2 CVBLY	642-878	850-885	893-1109	1263-1305	
PVGLF MUMPM	20-54	447-488						PVGL2 CVBM	642-878	850-885	893-1109	1263-1305	
PVGLF MUMPR	20-54	447-486						PVGL2 CVBQ	642-878	850-885	893-1109	1263-1305	
PVGLF MUMPS	151-178	428-511						PVGL2 CVBV	642-878	850-885	893-1109	1263-1305	
PVGLF NDVA	151-178	428-512						PVGL2 CVH22	770-916	1055-1112			
PVGLF NDVB	151-178	428-512						PVGL2 CVH4	643-864	1001-1117	1270-1315		
PVGLF NDVI	151-178	428-512						PVGL2 CVMA5	591-632	849-1079	1218-1293		
PVGLF NDVM	151-178	428-512						PVGL2 CVMLJH	502-543	850-978	1129-1174		
PVGLF NDVT	151-178	428-512						PVGL2 CVPF5	69-110	448-482	692-733	899-923	1040-1186
PVGLF NDVTG	151-178	428-512						PVGL2 CVPPU	69-110	448-480	690-731	897-921	1038-1184
PVGLF NDVU	151-178	428-512						PVGL2 CVPR8	224-258	468-509	695-699	816-862	1128-1165
PVGLF PHODV	36-93	221-282	309-336					PVGL2 CVPRM	224-258	468-509	695-699	816-862	1128-1165
PVGLF PI1HC	147-174	210-286						PVGL2 EBV	68-102				
PVGLF PI2H	90-117	141-175	238-266	483-528				PVGL2 FIPV	189-245	451-485	695-738	892-926	1043-1189
PVGLF PI2HG	90-117	141-175	238-266	483-528				PVGL2 IBV8	791-905	1067-1091			
PVGLF PI2HT	80-117	141-175	238-268	483-528				PVGL2 IBV8	437-478	772-804	1056-1080		
PVGLF PI3B	115-182	207-241	459-497					PVGL2 IBVD2	773-905	1067-1091			
PVGLF PI3H4	115-182	207-241	457-497					PVGL2 IBVK	437-478	772-804	1056-1080		
PVGLF RINDK	224-265	458-485						PVGL2 IBVM	437-478	772-804	1056-1080		
PVGLF RINDL	224-285	458-506						PVGLB HCMVA	43-88	128-162	436-484	844-878	
PVGLF SEND5	122-149	211-245	480-507					PVGLB HCMVT	22-88	128-162	437-485	845-879	
PVGLF SENDF	122-149	211-245	480-507					PVGLB HSV11	828-890				
PVGLF SENDH	122-149	211-245	480-507					PVGLB HSV1F	827-889				
PVGLF SENDJ	122-149	211-245	480-507					PVGLB HSV1K	827-889				
PVGLF SENDZ	122-149	211-245	480-507					PVGLB HSV1P	828-890				
PVGLF SV41	144-185	241-289	459-496					PVGLB HSV23	828-890				
PVGLF SV6	137-171	417-444						PVGLB HSV2H	828-890				
PVGLF TRTV	124-181	193-200	457-484					PVGLB HSV2S	817-871				
PVGLG BEFV	523-557							PVGLB HSV6U	37-71	195-223			
PVGLG BR5VC	92-123							PVGLB HSVB1	859-913				
PVGLG HR8V1	63-93							PVGLB HSVB2	440-474	848-902			
PVGLG HR8V4	66-107							PVGLB HSVBC	883-900				
PVGLG HRSV6	243-273							PVGLB HSE1	542-576	811-861			
PVGLG HRSV8	66-93							PVGLB HSE4	474-515	847-800			
PVGLG HSE4	271-298							PVGLB HSE4	542-576	811-861			
PVGLG HSEB	383-410							PVGLB HSEB	542-576	811-861			
PVGLG RABVT	489-519							PVGLB HSEB	542-576	811-861			
PVGLG VSVIG	472-499							PVGLB HSVEL	542-576	810-860			
PVGLH EBV	549-576	618-648						PVGLB HSVMD	380-435	648-683	787-845		
PVGLH HCMVA	107-136	270-297						PVGLB HSVSA	240-288	406-447			
PVGLH HCMVT	108-135							PVGLB MCMV6	206-260	427-475	883-778	860-894	
PVGLH HSV8G	62-89	360-403						PVGLB PRVIF	847-881				
PVGLH HSV8A	388-415							PVGLB VZVD	82-133	598-630	509-667		
PVGLI HCMVA	47-111							PVGLC HSV11	499-510				
PVGLM BUNGE	512-548	914-941	1128-1255					PVGLC HSV1K	488-510				
PVGLM BUNL7	913-950							PVGLC HSV2	442-476				
PVGLM BUNYW	340-374	504-535	682-709					PVGLC HSV23	443-477				
								PVGLC HSVBC	235-269				

PVGLM DUGSV	945-972						PVGLC HSEVB	182-218				
PVGLM HANTB	73-100	693-720					PVGLC HSEVB	63-87				
PVGLM HANTH	75-102						PVGLC HSEVB	62-88				
PVGLM HANTL	75-102						PVGLC HSEVB	63-87				
PVGLM HANTV	75-102						PVGLC HSEVB	183-235				
PVGLM PHV	69-86						PVGLC HSEVB	280-321				
PVGLM PUUMH	72-110						PVGLC HSEVB	280-321				
PVGLM PUUMS	72-110						PVGLD HSEVB	89-123				
PVGLM SEOUR	73-100	513-540	694-721				PVGLD HSEVB	138-173				
PVGLM SEOUS	73-100	513-540	694-721				PVGLD HSEVB	138-173				
PVGLM BEFV	523-584						PVGLD HSEVB	111-145				
PVGLP BEV	48-82	1145-1178	1184-1211	1505-1532			PVGLD HSEVB	111-159				
PVGLX HSEVB	17-44	413-444					PVGLF BRSA	146-202	504-545			
PVGLX PRVRI	427-481						PVGLF BRSA	146-202	267-302	506-547		
PVGLY JUNIN	14-41						PVGLF BRSA	146-202	267-302	506-554		
PVGLY LASSG	88-113						PVGLF CDVO	228-287	340-381	588-602		
PVGLY MOPEI	88-113	316-346					PVGLF HRSV1	116-203	267-302	506-549		
PVGLY PIARV	334-375						PVGLF HRSV1	116-202	267-302	506-549		
PVGLY TACV	109-136	315-350					PVGLF HRSV1	116-202	267-302	506-549		
PVGLY TACV6	303-338						PVGLF HRSV1	116-202	267-302	506-547		
PVGLY TACV7	302-337						PVGLF HRSV1	116-202	267-302	506-549		
PVGLY TACVT	303-338						PVGLF MEASE	116-184	228-269	482-500		
PVGLZ HSEVB	17-44						PVGLF MEASE	119-187	231-272	455-503		
PVGNM BPMV	403-430						PVGLF MEASY	116-184	228-269	452-500		
PVGNM CPBMV	182-221						PVGLF MUMPM	20-54	103-178	235-272	447-502	
PVGPB EBV	104-149						PVGLF MUMPM	20-54	103-179	235-272	447-502	
PVM1 REOVL	280-317						PVGLF MUMPS	20-54	103-179	235-272	447-502	
PVM21 REOVD	625-682						PVGLF NDVA	117-182	231-272	428-512		
PVM22 REOVD	624-681						PVGLF NDVB	122-182	231-272	428-517		
PVM2 REOVJ	824-881						PVGLF NDVI	133-182	238-272	428-517		
PVM3 REOVD	158-186	343-370	456-483	631-680			PVGLF NDVM	117-182	231-272	428-512		
PVMA2 BRSA	124-152						PVGLF NDVT	117-182	231-272	428-517		
PVMA2 HRSVA	124-151						PVGLF NDVTg	122-182	231-272	428-517		
PVMA2 BRSA	218-248						PVGLF NDVV	122-182	231-272	428-512		
PVMA2 HRSVA	218-248						PVGLF PHODV	29-83	187-266	308-350	533-581	
PVMA2 INCJJ	151-185						PVGLF PI1HC	123-174	207-267	458-503		
PVMA2 NDVA	247-274						PVGLF PI2H	83-183	477-528			
PVMA2 PI2HT	88-123						PVGLF PI2HG	83-183	477-528			
PVMA2 PI3B	201-231						PVGLF PI2HT	83-185	477-528			
PVMA2 PI3H4	201-231						PVGLF PI3B	117-182	207-241	458-518		
PVMA2 SV41	323-353						PVGLF PI3H4	117-182	207-241	462-532		
PVME1 CVBM	175-209						PVGLF RINDK	112-180	224-265	448-493		
PVME1 CVTKE	175-209						PVGLF RINDL	112-180	224-265	448-508		
PVME1 IBV6	21-48	184-218					PVGLF SEND5	127-188	211-271	463-533		
PVME1 IBV8	21-48	184-218					PVGLF SENDF	127-188	211-271	463-533		
PVME1 IBV2	21-48	184-218					PVGLF SENDH	127-188	218-271	463-533		
PVME1 IBVK		184-218					PVGLF SENDJ	127-188	211-271	463-533		
							PVGLF SENDZ	127-188	211-271	463-533		



PVMP_CAMVC	220-264	273-324			PVGLF_SV41	98-188	454-608				
PVMP_CAMVD	28-58	220-264	273-324		PVGLF_SV5	103-171	241-276	451-487			
PVMP_CAMVE		227-264	273-324		PVGLF_TRTV	105-161	180-224	457-498			
PVMP_CAMVN		220-264	273-324		PVGLG_BEV	508-812					
PVMP_CAMVS		220-264	273-324		PVGLG_BRVC	30-70	104-138				
PVMP_CAMVW		220-264	273-324		PVGLG_HRSV1	30-81					
PVMP_CERV	28-53	100-127			PVGLG_HRSV2	30-85					
PVMP_SOCMV	4-31	78-118			PVGLG_HRSV3	30-85					
PVMSA_HPBHE	284-328				PVGLG_HRSV4	30-107					
PVMT1_DHV1	38-65	237-264			PVGLG_HRSV5	30-85					
PVMT8_MYXVL	163-180				PVGLG_HRSV6	30-85					
PVMT9_MYXVL	485-492				PVGLG_HRSV7	30-85					
					PVGLG_HRSV8	30-81					
					PVGLG_HRSVA	30-67					
					PVGLG_HRSVL	25-85					
					PVGLG_HSVE4	271-305					
					PVGLG_SIGMA	344-381	484-498				
					PVGLG_GYNU	488-523					
					PVGLG_VHSV0	363-387					
					PVGLG_VSVIG	478-510					
					PVGLH_EBV	53-87	160-201	338-380	853-894		
					PVGLH_HCMVA	103-137	270-311	693-741			
					PVGLH_HCMVT	102-136	692-740				
					PVGLH_HSV11	447-481					
					PVGLH_HSV1E	447-481					
					PVGLH_HSV8G	357-408					
					PVGLH_HSVBC	384-418					
					PVGLH_HSVE4	334-378	414-455				
					PVGLH_HSVEB	327-372	407-448				
					PVGLH_HSVSA	32-86	374-453	864-712			
					PVGLH_HCMVS	440-474					
					PVGLH_PRVKA	228-260					
					PVGLH_PRVN3	228-260					
					PVGLH_PRVRI	228-260					
					PVGLH_VZVD	455-508					
					PVGLI_HCMVA	47-111	323-359				
					PVGLM_BUNGE	612-667	686-737	1228-1262			
					PVGLM_BUNL7	643-677	918-950				
					PVGLM_BUNSH	643-677					
					PVGLM_BUNYW	340-374	504-563	905-939			
					PVGLM_DUGBV	837-889	1238-1300				
					PVGLM_HANTB	693-727					
					PVGLM_HANTH	72-108					
					PVGLM_HANTL	72-108					
					PVGLM_HANTV	72-108					
					PVGLM_PHV	73-111					
					PVGLM_PTPV	149-251					



	PVGLM SEOUR	694-728							
	PVGLM SEOUS	693-730							
	PVGILN BEFV	377-414	513-569						
	PVGLP BEV	43-82	80-124	622-656	1128-1238				
	PVGLX HSEB	177-262							
	PVGLX PRVI	420-481							
	PVGLY JUNIN	301-349							
	PVGLY LASSG	317-380	388-422						
	PVGLY LASSJ	318-361	388-423						
	PVGLY LYCVA	333-387	385-432						
	PVGLY LYCVW	124-158	333-387	395-432					
	PVGLY MOPEI	316-359							
	PVGLY PIARV	334-375							
	PVGLY TACV	315-383							
	PVGLY TACV5	303-351	382-416						
	PVGLY TACV7	302-350	381-415						
	PVGLY TACVT	303-351	382-416						
	PVGNB CPMV	835-888							
	PVGNM BPMV	143-177	403-437						
	PVGNM CFMV	180-201							
	PVGNM CP8MV	192-226	758-792	874-915					
	PVGNM RCMV	837-871	812-848						
	PVGP8 EBV	84-149							
	PVM01 VACC	5-58							
	PVM1 REOVL	287-321							
	PVM21 REOVD	416-450	618-683						
	PVM22 REOVD	416-450	618-682						
	PVM2 REOVJ	416-450	618-682						
	PVM2 REOVL	416-450	618-682						
	PVM3 REOVD	135-190	337-371	523-558	618-690				
	PVMA2 BR5VA	42-80							
	PVMA2 HR5VA	42-80							
	PVMAT CDVO	193-234							
	PVMAT INCJJ	73-114	151-208						
	PVMAT NDVA	310-358							
	PVMAT NDB8	324-358							
	PVMAT Pj3B	98-133	204-252						
	PVMAT Pj3H4	98-133	204-252						
	PVMAT RABVA	88-103							
	PVMAT RABVC	88-103							
	PVMAT RABVE	88-103							
	PVMAT RABVN	88-103							
	PVMAT RABVP	88-103							
	PVMAT RABVS	88-103							
	PVMAT SYNIV	246-280							
	PVMAT VSUIG	188-232							
	PVME1 CV8IM	175-209							

	PVME1_CVPFS	88-148	212-257						
	PVME1_CVPPU	212-257							
	PVME1_GVPRM	212-257							
	PVME1_CVTKE	28-82	176-208						
	PVME1_FIPV	212-267							
	PVME1_BVB6	21-55	177-218						
	PVME1_BVB	21-55	177-218						
	PVME1_BVB2	21-55	177-218						
	PVME1_BVK	38-94							
	PVMP_CAMVC	187-254	270-324						
	PVMP_CAMVD	187-254	270-324						
	PVMP_CAMVE	187-254	270-324						
	PVMP_CAMVN	187-254	270-324						
	PVMP_CAMV8	187-254	270-324						
	PVMP_CAMVV	187-254	270-324						
	PVMP_CERV	212-248							
	PVMP_FMVD	217-261							
	PVMP_SOCMV	78-118							
	PVMSA_HPBDB	272-313	324-381						
	PVMSA_HPBDG	271-312	323-380						
	PVMSA_HPBDU	234-276	289-323						
	PVMSA_HPBDW	272-313	324-381						
	PVMSA_HPBG8	210-244							
	PVMSA_HPBHE	284-328							
	PVMSA_WHV1	208-242							
	PVMSA_WHV59	213-247							
	PVMSA_WHV7	213-247							
	PVMSA_WHVI	213-247							
	PVMT1_DHV11	201-235							
	PVMT1_IANN	82-128	174-222						
	PVMT1_IABAN	82-128	174-222						
	PVMT1_IACAO	31-78							
	PVMT1_IAFOW	82-128	174-222						
	PVMT1_IAFRP	82-128	174-222						
	PVMT1_IAPFW	82-128	174-222						
	PVMT1_IALB1	82-128	174-222						
	PVMT1_IALB2	82-128	174-222						
	PVMT1_IAMAN	82-128	174-222						
	PVMT1_IAPOC	82-128	174-222						
	PVMT1_IARUE	82-128	174-222						
	PVMT1_IAUDO	82-128	174-222						
	PVMT1_IAWIL	82-128	174-222						
	PVMT1_IAZI1	82-128	174-222						
	PVMT1_INBAC	176-208							
	PVMT1_INBAD	176-208							
	PVMT1_INBLE	176-208							
	PVMT1_INBSI	176-208							

[illegible]

**TABLE VI**

Search Results Summary for PCTLZIP,  
P1CTLZIP, and P2CTLZIP Motifs

PCTZIP	P1CTLZIP	P2CTLZIP							
LIBRARY FILE	LIBRARY FILE	LIBRARY FILE							
PENV FOAMV	PENV BIV06	PENV BIV06	434-450					525-542	
PENV HV1MA	PENV BIV27	PENV BIV27	483-478					554-571	
PENV HV1MF	PENV FOAMV	PENV FENV1	481-498	864-860				630-647	
PENV HV1RH	PENV HV1KB	PENV FIVPE	752-788					781-788	
PENV HV1RC	PENV HV1MA	PENV FIVSD	437-453					779-798	
PENV HV122	PENV HV1MF	PENV FIVT2	183-188					780-787	
PENV HV12H	PENV HV1RH	PENV FLVCL	444-460					624-841	
PENV HV2BE	PENV HV1S1	PENV FLVGL	738-754					38-55	
PENV HV2D1	PENV HV1SC	PENV FLVLB	186-201					605-622	
PENV HV2G1	PENV HV122	PENV FLVSA	123-138					625-842	
PENV HV2N2	PENV HV123	PENV FOAMV	117-133					602-619	
PENV HV2RO	PENV HV1ZH	PENV FSVGA	437-453					710-727	957-974
PENV HV2SB	PENV HV2BE	PENV FSVGB	750-765					625-842	
PENV HV2ST	PENV HV2D1	PENV FSVSM	741-756					608-625	
PENV JSRV	PENV HV2G1	PENV HV1QY	741-756					123-140	
PENV MMTVB	PENV HV2NZ	PENV HV122	742-757					410-427	
PENV MMTVG	PENV HV2RO	PENV HV123	751-766					154-171	
PENV SIVMK	PENV HV2SB	PENV HV2CA	743-758					750-767	
PENV SIVML	PENV HV2ST	PENV MCFF	746-760					600-617	
PHEMA CVBLY	PENV JSRV	PENV MCFF3	104-119	541-557				601-618	
PHEMA CVBM	PENV MCFF	PENV MLVAV	397-413					630-647	
PHEMA CVBQ	PENV MCFF3	PENV MLVCB	397-413					625-842	
PHEMA CVHOC	PENV MLVAV	PENV MLVFB	427-443					639-656	
PHEMA CVMA5	PENV MLVCB	PENV MLVFF	422-438					638-656	
PHEMA CVMS	PENV MLVHO	PENV MLVFP	423-439					639-656	
PHEMA INBAA	PENV MLVMO	PENV MLVHO	428-442					628-643	
PHEMA INBBE	PENV MLVRD	PENV MLVKI	424-440					167-184	
PHEMA INBBO	PENV MLVRK	PENV MLVMO	424-440					628-646	
PHEMA INBEN	PENV MMTVB	PENV MLVRD	618-633					624-841	
PHEMA INBFU	PENV MMTVG	PENV MLVRK	618-633					624-841	
PHEMA INBGL	PENV SFV1	PENV MSVFB	884-880					170-187	
PHEMA INBHK	PENV SFV3L	PENV RMCFF	861-877					603-620	
PHEMA INBIB	PENV SIVGB	PENV SFV1	93-109					710-727	957-974
PHEMA INBID	PENV SIVMK	PENV SFV3L	139-154	802-818				707-724	954-971
PHEMA INBLE	PENV SIVML	PENV SIVM1	139-154	801-817				768-783	
PHEMA INBMD	PENV SIVS4	PENV SIVMK	808-822					785-782	
PHEMA INBME	PENV SIVSP	PENV SIVML	810-828					784-781	
PHEMA INBNA	PHEMA CDVO	PENV SIVS4	36-52					789-786	
PHEMA INBOR	PHEMA CVBLY	PENV SIVSP	391-406					773-780	
PHEMA INBSI	PHEMA CVBM	PENV SMRVH	391-406					538-553	
PHEMA INBSJ	PHEMA CVBQ	PENV SMSAV	391-406					42-58	
PHEMA INBUS	PHEMA CVHOC	PHEMA CDVO	391-406					36-53	200-217
PHEMA INBVI	PHEMA CVMA5	PHEMA CVBLY	402-417					391-408	
PHEMA INBVK	PHEMA CVMS	PHEMA CVBM	403-418					391-408	
PHEMA INBYB	PHEMA IAAIC	PHEMA CVBQ	237-253					391-408	

PHEMA MUMPM	133-148		PHEMA_IABAN	221-237			PHEMA_CVHOC	391-408
PHEMA MUMPR	133-148		PHEMA_IABUD	234-250			PHEMA_IAAIC	322-339
PHEMA MUMPS	133-148		PHEMA_IACKA	234-250			PHEMA_IABAN	306-323
PHEMA PI1HW	345-380		PHEMA_IACKG	231-247			PHEMA_IABUD	320-337
PHEMA PI2H	65-80		PHEMA_IACKV	230-246			PHEMA_IACKA	320-337
PHEMA PI2HT	65-80		PHEMA_IADA1	234-250			PHEMA_IACKG	316-333
PHEMA RINDK	368-383		PHEMA_IADA3	237-253			PHEMA_IACKP	302-319
PHEMA SV5	7-84		PHEMA_IADCZ	234-250			PHEMA_IACKQ	302-319
PHEMA SV5CM	7-84		PHEMA_IADH1	221-237			PHEMA_IACKS	319-336
PHEMA SV5CP	7-84		PHEMA_IADH2	221-237			PHEMA_IACKV	315-332
PHEMA SV5ELN	7-84		PHEMA_IADH3	221-237			PHEMA_IADA1	320-337
PVENV DHV11	42-57		PHEMA_IADH4	221-237			PHEMA_IADA3	322-339
PVFP7 CAPVK	88-104		PHEMA_IADH5	221-237			PHEMA_IADCZ	320-337
PVFUS VACC8	72-87		PHEMA_IADH6	221-237			PHEMA_IADH1	306-323
PVG01 BPP22	242-257		PHEMA_IADH7	221-237			PHEMA_IADH2	306-323
PVG01 HSEB	189-184		PHEMA_IADM2	237-253			PHEMA_IADH3	306-323
PVG01 HSV11	210-225	317-332	PHEMA_IADN2	234-250			PHEMA_IADH4	306-323
PVG06 BPT4	184-188		PHEMA_IADN6	221-237			PHEMA_IADH6	306-323
PVG07 BPT4	885-900		PHEMA_IADN7	237-253			PHEMA_IADH7	306-323
PVG08 HSV11	134-149		PHEMA_IADN8	230-246			PHEMA_IADN2	322-339
PVG10 BPPH2	183-188		PHEMA_IADN9	236-252			PHEMA_IADN3	320-337
PVG10 BPPZA	183-188		PHEMA_IADN10	235-251			PHEMA_IADN4	322-339
PVG10 HSVSA	108-124		PHEMA_IADN11	230-246			PHEMA_IADN5	306-323
PVG16 BPP1	81-86		PHEMA_IADN12	230-246			PHEMA_IADN6	322-339
PVG18 BPT4	468-483		PHEMA_IADN13	230-246			PHEMA_IADN7	315-332
PVG25 BPT4	87-112		PHEMA_IADN14	230-246			PHEMA_IADN8	320-337
PVG29 HSV11	20-35		PHEMA_IADN15	236-252			PHEMA_IADN9	319-336
PVG30 BPPH8	11-84		PHEMA_IADN16	236-252			PHEMA_IADN10	321-338
PVG36 BPOX2	22-37		PHEMA_IADN17	236-252			PHEMA_IADN11	315-332
PVG36 HSVSA	108-123		PHEMA_IADN18	230-246			PHEMA_IADN12	315-332
PVG37 BPT2	1263-1268		PHEMA_IADN19	230-246			PHEMA_IADN13	315-332
PVG37 HSV11	284-289		PHEMA_IADN20	236-252			PHEMA_IADN14	315-332
PVG55 HSV11	22-37	143-158	PHEMA_IADN21	236-252			PHEMA_IADN15	321-338
PVG58 HSV11	288-283		PHEMA_IADN22	236-252			PHEMA_IADN16	321-338
PVG68 HSV11	102-117		PHEMA_IADN23	236-252			PHEMA_IADN17	321-338
PVG68 HSV11	287-282		PHEMA_IADN24	230-246			PHEMA_IADN18	315-332
PVG65 HSV11	518-533		PHEMA_IADN25	230-246			PHEMA_IADN19	315-332
PVG8 BPPH2	234-249		PHEMA_IADN26	236-252			PHEMA_IADN20	321-338
PVG8 BPPZA	234-249		PHEMA_IADN27	236-252			PHEMA_IADN21	321-338
PVG8 SPV1R	57-72		PHEMA_IADN28	236-252			PHEMA_IADN22	315-332
PVG8 BPPH8	234-249		PHEMA_IADN29	236-252			PHEMA_IADN23	321-338
PVG8 BPPH8	234-249		PHEMA_IADN30	236-252			PHEMA_IADN24	315-332
PVG8 BPPH8	234-249		PHEMA_IADN31	236-252			PHEMA_IADN25	321-338
PVG8 BPPH8	234-249		PHEMA_IADN32	236-252			PHEMA_IADN26	315-332
PVG8 BPPH8	234-249		PHEMA_IADN33	236-252			PHEMA_IADN27	321-338
PVG8 BPPH8	234-249		PHEMA_IADN34	236-252			PHEMA_IADN28	315-332
PVG8 BPPH8	234-249		PHEMA_IADN35	236-252			PHEMA_IADN29	315-332
PVG8 BPPH8	234-249		PHEMA_IADN36	236-252			PHEMA_IADN30	321-338
PVG8 BPPH8	234-249		PHEMA_IADN37	236-252			PHEMA_IADN31	315-332
PVG8 BPPH8	234-249		PHEMA_IADN38	236-252			PHEMA_IADN32	321-338
PVG8 BPPH8	234-249		PHEMA_IADN39	236-252			PHEMA_IADN33	315-332
PVG8 BPPH8	234-249		PHEMA_IADN40	236-252			PHEMA_IADN34	321-338
PVG8 BPPH8	234-249		PHEMA_IADN41	236-252			PHEMA_IADN35	315-332
PVG8 BPPH8	234-249		PHEMA_IADN42	236-252			PHEMA_IADN36	321-338
PVG8 BPPH8	234-249		PHEMA_IADN43	236-252			PHEMA_IADN37	315-332
PVG8 BPPH8	234-249		PHEMA_IADN44	236-252			PHEMA_IADN38	315-332
PVG8 BPPH8	234-249		PHEMA_IADN45	236-252			PHEMA_IADN39	321-338
PVG8 BPPH8	234-249		PHEMA_IADN46	236-252			PHEMA_IADN40	315-332
PVG8 BPPH8	234-249		PHEMA_IADN47	236-252			PHEMA_IADN41	321-338
PVG8 BPPH8	234-249		PHEMA_IADN48	236-252			PHEMA_IADN42	315-332
PVG8 BPPH8	234-249		PHEMA_IADN49	236-252			PHEMA_IADN43	321-338
PVG8 BPPH8	234-249		PHEMA_IADN50	236-252			PHEMA_IADN44	315-332
PVG8 BPPH8	234-249		PHEMA_IADN51	236-252			PHEMA_IADN45	321-338
PVG8 BPPH8	234-249		PHEMA_IADN52	236-252			PHEMA_IADN46	315-332
PVG8 BPPH8	234-249		PHEMA_IADN53	236-252			PHEMA_IADN47	321-338
PVG8 BPPH8	234-249		PHEMA_IADN54	236-252			PHEMA_IADN48	315-332
PVG8 BPPH8	234-249		PHEMA_IADN55	236-252			PHEMA_IADN49	321-338
PVG8 BPPH8	234-249		PHEMA_IADN56	236-252			PHEMA_IADN50	315-332
PVG8 BPPH8	234-249		PHEMA_IADN57	236-252			PHEMA_IADN51	321-338
PVG8 BPPH8	234-249		PHEMA_IADN58	236-252			PHEMA_IADN52	315-332
PVG8 BPPH8	234-249		PHEMA_IADN59	236-252			PHEMA_IADN53	321-338
PVG8 BPPH8	234-249		PHEMA_IADN60	236-252			PHEMA_IADN54	315-332
PVG8 BPPH8	234-249		PHEMA_IADN61	236-252			PHEMA_IADN55	321-338
PVG8 BPPH8	234-249		PHEMA_IADN62	236-252			PHEMA_IADN56	315-332
PVG8 BPPH8	234-249		PHEMA_IADN63	236-252			PHEMA_IADN57	321-338
PVG8 BPPH8	234-249		PHEMA_IADN64	236-252			PHEMA_IADN58	315-332
PVG8 BPPH8	234-249		PHEMA_IADN65	236-252			PHEMA_IADN59	321-338
PVG8 BPPH8	234-249		PHEMA_IADN66	236-252			PHEMA_IADN60	315-332
PVG8 BPPH8	234-249		PHEMA_IADN67	236-252			PHEMA_IADN61	321-338
PVG8 BPPH8	234-249		PHEMA_IADN68	236-252			PHEMA_IADN62	315-332
PVG8 BPPH8	234-249		PHEMA_IADN69	236-252			PHEMA_IADN63	321-338
PVG8 BPPH8	234-249		PHEMA_IADN70	236-252			PHEMA_IADN64	315-332
PVG8 BPPH8	234-249		PHEMA_IADN71	236-252			PHEMA_IADN65	321-338
PVG8 BPPH8	234-249		PHEMA_IADN72	236-252			PHEMA_IADN66	315-332
PVG8 BPPH8	234-249		PHEMA_IADN73	236-252			PHEMA_IADN67	321-338
PVG8 BPPH8	234-249		PHEMA_IADN74	236-252			PHEMA_IADN68	315-332
PVG8 BPPH8	234-249		PHEMA_IADN75	236-252			PHEMA_IADN69	321-338
PVG8 BPPH8	234-249		PHEMA_IADN76	236-252			PHEMA_IADN70	315-332
PVG8 BPPH8	234-249		PHEMA_IADN77	236-252			PHEMA_IADN71	321-338
PVG8 BPPH8	234-249		PHEMA_IADN78	236-252			PHEMA_IADN72	315-332
PVG8 BPPH8	234-249		PHEMA_IADN79	236-252			PHEMA_IADN73	321-338
PVG8 BPPH8	234-249		PHEMA_IADN80	236-252			PHEMA_IADN74	315-332
PVG8 BPPH8	234-249		PHEMA_IADN81	236-252			PHEMA_IADN75	321-338
PVG8 BPPH8	234-249		PHEMA_IADN82	236-252			PHEMA_IADN76	315-332
PVG8 BPPH8	234-249		PHEMA_IADN83	236-252			PHEMA_IADN77	321-338
PVG8 BPPH8	234-249		PHEMA_IADN84	236-252			PHEMA_IADN78	315-332
PVG8 BPPH8	234-249		PHEMA_IADN85	236-252			PHEMA_IADN79	321-338
PVG8 BPPH8	234-249		PHEMA_IADN86	236-252			PHEMA_IADN80	315-332
PVG8 BPPH8	234-249		PHEMA_IADN87	236-252			PHEMA_IADN81	321-338
PVG8 BPPH8	234-249		PHEMA_IADN88	236-252			PHEMA_IADN82	315-332
PVG8 BPPH8	234-249		PHEMA_IADN89	236-252			PHEMA_IADN83	321-338
PVG8 BPPH8	234-249		PHEMA_IADN90	236-252			PHEMA_IADN84	315-332
PVG8 BPPH8	234-249		PHEMA_IADN91	236-252			PHEMA_IADN85	321-338
PVG8 BPPH8	234-249		PHEMA_IADN92	236-252			PHEMA_IADN86	315-332
PVG8 BPPH8	234-249		PHEMA_IADN93	236-252			PHEMA_IADN87	321-338
PVG8 BPPH8	234-249		PHEMA_IADN94	236-252			PHEMA_IADN88	315-332
PVG8 BPPH8	234-249		PHEMA_IADN95	236-252			PHEMA_IADN89	321-338
PVG8 BPPH8	234-249		PHEMA_IADN96	236-252			PHEMA_IADN90	315-332
PVG8 BPPH8	234-249		PHEMA_IADN97	236-252			PHEMA_IADN91	321-338
PVG8 BPPH8	234-249		PHEMA_IADN98	236-252			PHEMA_IADN92	315-332
PVG8 BPPH8	234-249		PHEMA_IADN99	236-252			PHEMA_IADN93	321-338
PVG8 BPPH8	234-249		PHEMA_IADN100	236-252			PHEMA_IADN94	315-332
PVG8 BPPH8	234-249		PHEMA_IADN101	236-252			PHEMA_IADN95	321-338
PVG8 BPPH8	234-249		PHEMA_IADN102	236-252			PHEMA_IADN96	315-332
PVG8 BPPH8	234-249		PHEMA_IADN103	236-252			PHEMA_IADN97	321-338
PVG8 BPPH8	234-249		PHEMA_IADN104	236-252			PHEMA_IADN98	315-332
PVG8 BPPH8	234-249		PHEMA_IADN105	236-252			PHEMA_IADN99	321-338
PVG8 BPPH8	234-249		PHEMA_IADN106	236-252			PHEMA_IADN100	315-332
PVG8 BPPH8	234-249		PHEMA_IADN107	236-252			PHEMA_IADN101	321-338
PVG8 BPPH8	234-249		PHEMA_IADN108	236-252			PHEMA_IADN102	315-332
PVG8 BPPH8	234-249		PHEMA_IADN109	236-252			PHEMA_IADN103	321-338
PVG8 BPPH8	234-249		PHEMA_IADN110	236-252			PHEMA_IADN104	315-332
PVG8 BPPH8	234-249		PHEMA_IADN111	236-252			PHEMA_IADN105	321-338
PVG8 BPPH8	234-249		PHEMA_IADN112	236-252			PHEMA_IADN106	315-332
PVG8 BPPH8	234-249		PHEMA_IADN113	236-252			PHEMA_IADN107	321-338
PVG8 BPPH8	234-249		PHEMA_IADN114	236-252			PHEMA_IADN108	315-332
PVG8 BPPH8	234-249		PHEMA_IADN115	236-252			PHEMA_IADN109	321-338
PVG8 BPPH8	234-249		PHEMA_IADN116	236-252			PHEMA_IADN110	315-332
PVG8 BPPH8	234-249		PHEMA_IADN117	236-252			PHEMA_IADN111	321-338
PVG8 BPPH8	234-249		PHEMA_IADN118	236-252			PHEMA_IADN112	315-332
PVG8 BPPH8	234-249		PHEMA_IADN119	236-252			PHEMA_IADN113	321-338
PVG8 BPPH8	234-249		PHEMA_IADN120	236-252			PHEMA_IADN114	315-332
PVG8 BPPH8	234-249		PHEMA_IADN121	236-252			PHEMA_IADN115	321-338
PVG8 BPPH8	234-249		PHEMA_IADN122	236-252			PHEMA_IADN116	315-332
PVG8 BPPH8	234-249		PHEMA_IADN123	236-252			PHEMA_IADN117	321-338
PVG8 BPPH8	234-249		PHEMA_IADN124	236-252			PHEMA_IADN118	315-332
PVG8 BPPH8	234-249		PHEMA_IADN125	236-252			PHEMA_IADN119	321-338
PVG8 BPPH8	234-249		PHEMA_IADN126	236-252			PHEMA_IADN120	315-332
PVG8 BPPH8	234-249		PHEMA_IADN127	236-252			PHEMA_IADN121	321-338
PVG8 BPPH8	234-249		PHEMA_IADN128	236-252			PHEMA_IADN122	315-332

PVGL2_CVPR5	442-457		PHEMA_IAME6	221-237				PHEMA_IATHTO	321-338	
PVGL2_CVPRU	440-455	504-519	PHEMA_IAMIN	85-101	231-247			PHEMA_IATUR	321-338	
PVGL2_CVPR8	218-233		PHEMA_IANT6	237-253				PHEMA_IJAP	317-334	
PVGL2_CVPRM	218-233		PHEMA_IACU7	221-237				PHEMA_IAMAA	318-336	
PVGL2_IBV6	1056-1071		PHEMA_IARUD	234-250				PHEMA_IAMAB	324-341	
PVGL2_IBV8	1055-1070		PHEMA_IASE2	234-250				PHEMA_IAMAO	322-339	
PVGL2_IBVD2	1056-1071		PHEMA_IASH2	234-250				PHEMA_IAME1	322-339	
PVGL2_IBVK	1055-1070		PHEMA_IASTA	230-246				PHEMA_IAME2	322-339	
PVGL2_IBVM	1055-1070		PHEMA_IATAI	235-261				PHEMA_IAME8	308-323	
PVGLB_HSVSA	701-716		PHEMA_IATKM	234-250				PHEMA_IAMIN	316-333	
PVGLB_PRVIF	203-218		PHEMA_IATKO	233-249				PHEMA_IANT6	322-339	
PVGLC_HSVBC	475-490		PHEMA_IATKR	230-248				PHEMA_IAPIL	320-337	
PVGLC_HSVE4	444-459		PHEMA_IATKW	229-245				PHEMA_IACU7	306-323	
PVGLC_HSVEB	427-442		PHEMA_IAUDO	237-253				PHEMA_IARUD	320-337	
PVGLC_PRVIF	446-461		PHEMA_IAUSS	235-251				PHEMA_IASE2	320-337	
PVGLD_HSV11	78-94		PHEMA_IACU7	238-254				PHEMA_IASH2	321-338	
PVGLD_HSV2	78-94		PHEMA_IAXIA	235-251				PHEMA_IASTA	315-332	
PVGLF_BR5VA	265-280		PHEMA_IACZO	237-253				PHEMA_IATKM	320-337	
PVGLF_BR5VC	265-280		PHEMA_IASH2	221-237				PHEMA_IAUDO	322-339	350-387
PVGLF_BR5VR	265-280		PHEMA_IASH3	221-237				PHEMA_IACU7	323-340	
PVGLF_HRSV1	265-280		PHEMA_IACU7	237-253				PHEMA_IACZO	322-339	
PVGLF_HRSVA	265-280		PHEMA_INBAA	115-131	285-310			PHEMA_IASH2	306-323	
PVGLF_HRSVL	265-280		PHEMA_INBDE	123-139	303-318			PHEMA_IASH3	306-323	
PVGLF_HRSVR	265-280		PHEMA_INBBO	116-132	283-308			PHEMA_IACU7	322-339	
PVGLF_MUMPS	5-84		PHEMA_INBEN	123-139	301-316			PHEMA_IACU7	322-339	
PVGLI_VZVD	278-293		PHEMA_INBFU	108-124	288-301			PHEMA_IACU7	322-339	
PVGLM_HANTB	900-915		PHEMA_INBGL	110-135	286-311			PHEMA_IACU7	322-339	
PVGLM_PTPV	743-758		PHEMA_INBHK	116-132	283-308			PHEMA_IACU7	322-339	
PVGLM_SEOUR	901-916		PHEMA_INBIB	108-124	288-303			PHEMA_IACU7	322-339	
PVGLM_SEOUS	900-915		PHEMA_INBID	120-138	289-314			PHEMA_IACU7	322-339	
PVGLY_LAS9G	426-441		PHEMA_INBLE	123-139	302-317			PHEMA_IACU7	322-339	
PVGLY_LAS6J	427-442		PHEMA_INBMD	113-129	282-307			PHEMA_IACU7	322-339	
PVGLY_MOPEI	425-440		PHEMA_INBME	116-132	286-311			PHEMA_IACU7	322-339	
PVM3_REOVD	521-536		PHEMA_INBNA	108-124	288-303			PHEMA_IACU7	322-339	
PVMSA_HPBGS	380-396		PHEMA_INBOR	123-139	301-316			PHEMA_IACU7	322-339	
PVMSA_HPBV9	187-202		PHEMA_INBBI	123-139	301-316			PHEMA_IACU7	322-339	
PVMSA_WHV1	378-393		PHEMA_INBSJ	110-135	288-313			PHEMA_IACU7	322-339	
PVMSA_WHV68	383-398		PHEMA_INBUS	116-132	284-309			PHEMA_IACU7	322-339	
PVMSA_WHV7	383-398		PHEMA_INBVI	116-132	286-311			PHEMA_IACU7	322-339	
PVMSA_WHV8	383-398		PHEMA_INBVK	123-139	303-318			PHEMA_IACU7	322-339	
PVMSA_WHV8I	383-398		PHEMA_INBYB	108-124	286-301			PHEMA_IACU7	322-339	
PVMSA_WHVW6	234-249		PHEMA_IACU7	133-148				PHEMA_IACU7	322-339	
PVMT2_IANN	25-40		PHEMA_IACU7	133-148				PHEMA_IACU7	322-339	
PVMT2_IABAN	25-40		PHEMA_IACU7	133-148				PHEMA_IACU7	322-339	
PVMT2_IACOW	25-40		PHEMA_IACU7	345-360				PHEMA_IACU7	322-339	
PVMT2_IAPFR	25-40		PHEMA_IACU7	85-81				PHEMA_IACU7	322-339	
PVMT2_IAPRW	25-40		PHEMA_IACU7	85-81				PHEMA_IACU7	322-339	

PVMT2 IALE1	25-40	PHEMA P13B	324-340				PHEMA SV41	85-102	
PVMT2 IALE2	25-40	PHEMA P13H4	324-340				PHEMA SV5	84-101	
PVMT2 IAMAN	25-40	PHEMA P13HA	324-340				PHEMA SV6CM	84-101	
PVMT2 IAPUE	25-40	PHEMA P13HT	324-340				PHEMA SV6CP	84-101	
PVMT2 IASIN	25-40	PHEMA P13HU	324-340				PHEMA SV6LN	84-101	
PVMT2 IAUDD	25-40	PHEMA P13HV	324-340				PVF05 VACCC	280-287	
PVMT2 IAWIL	25-40	PHEMA P13HW	324-340				PVF05 VACCP	280-287	
PVMT9 MYXVL	228-241	PHEMA P13HX	324-340				PVF05 VACCV	281-288	
		PHEMA RINDK	368-383				PVF09 VACCC	178-193	
		PHEMA SV6	7-94				PVF09 VACCV	178-193	
		PHEMA SV6CM	7-94				PVG27 HSVSA	208-226	
		PHEMA SV6CP	7-94				PVG28 HSVI1	173-190	
		PHEMA SV6LN	7-94				PVG39 HSVI1	848-885	
		PVENV DHV11	42-57				PVG43 HSVI1	108-126	521-538
		PVENV EAV	25-41				PVG67 HSVI1	171-188	
		PVFP2 FOWPV	88-104				PVG72 HSVI1	1252-1289	
		PVFP7 CAPVK	89-104				PVGf1 IBVB	3073-3080	
		PVFUS VACC8	72-87				PVGL2 IBV8	1084-1111	
		PVG01 HSVEB	188-184				PVGLB HSVI1	738-753	
		PVG01 HSVI1	208-225	317-332			PVGLB HSVI4	675-692	
		PVG08 HSVI1	134-149				PVGLB HSVI4	738-753	
		PVG10 HSVSA	108-124				PVGLB HSVI4	738-753	
		PVG11 HSVI1	103-119				PVGLB HSVI4	738-753	
		PVG12 HSVI1	270-288				PVGLB ILTV6	597-614	
		PVG1 SPVIR	76-92				PVGLB ILTV8	607-624	
		PVG29 HSVI1	20-35				PVGLB ILTVT	607-624	
		PVG38 BPOX2	22-37				PVGLC PRVIF	180-197	
		PVG38 HSVSA	108-123				PVGLC VZVD	488-488	
		PVG37 HSVI1	284-289				PVGLF SV6	401-418	
		PVG41 HSVI1	244-280				PVGLH HCMVA	385-382	
		PVG48 HSVI1	1244-1260				PVGLH HCMVT	384-381	
		PVG55 HSVI1	22-37	143-168			PVGLH HSVI1	245-262	803-820
		PVG58 HSVI1	208-283				PVGLH HSVI1	245-262	803-820
		PVG58 HSVI1	101-117				PVGLI HSVI1	43-60	
		PVG68 HSVSA	130-146	330-346			PVGLM BUNL7	81-98	
		PVG69 HSVI1	287-282				PVGLM BUNSH	81-98	
		PVG65 HSVI1	382-378	518-533			PVGLM PUUMH	712-729	
		PVG71 HSVSA	89-105				PVGLM PUUMS	712-729	
		PVG9 BPPH2	234-249				PVGLM RVFV	344-381	
		PVG9 BPPZA	234-249				PVGLM RVFVZ	344-381	
		PVG9 SPVIR	57-72				PVGLY LASSG	12-94	
		PVGf1 IBVB	2210-2228				PVGLY LASSJ	12-94	
		PVGL2 CVBF	123-139	174-180	284-279		PVGLY LYCVA	12-94	
		PVGL2 CVBL9	123-139	174-180	284-279		PVGLY LYCVW	12-94	
		PVGL2 CVBLY	123-139	174-180	284-279		PVGLY MOPEI	12-94	
		PVGL2 CVBM	123-139	174-180	284-279		PVGLY MOPEI	280-287	
		PVGL2 CVBQ	31-47	123-139	174-180	284-279	PVGLY MOPEI	280-287	



		PVGL2_CVBV	123-139	174-180	264-279	PVMAT_CDVO	148-166
		PVGL2_CVM4	95-111	1287-1283		PVMAT_MEAS1	87-104
		PVGL2_CVMA5	96-111	1216-1231		PVMP_CAMVC	147-164
		PVGL2_CVMJH	95-111	1126-1142		PVMP_CAMVD	147-164
		PVGL2_CVPFS	442-457	800-816	1274-1280	PVMP_CAMVE	147-164
		PVGL2_CVPPU	440-455	504-518	788-814	PVMP_CAMVN	147-164
		PVGL2_CVPR8	218-233	578-592	1050-1068	PVMP_CAMVS	147-164
		PVGL2_CVPRM	218-233	578-592	1050-1068	PVMP_CAMVW	147-164
		PVGL2_FIPV	803-819	1277-1293		PVMSA_HPBVO	11-94
		PVGL2_BIV6	1056-1071			PVMSA_HPBV2	185-202
		PVGL2_BIV8	1055-1070			PVMSA_HPBV4	185-202
		PVGL2_IBVD2	1056-1071			PVMSA_HPBVA	174-191
		PVGL2_BVK	1055-1070			PVMSA_HPBVD	11-94
		PVGL2_IBVM	1055-1070			PVMSA_HPBVJ	174-191
		PVGLB_HSV9A	701-716			PVMSA_HPBVL	174-191
		PVGLB_PRVIF	203-218			PVMSA_HPBVN	11-94
		PVGLB_VZVD	522-538			PVMSA_HPBVO	174-191
		PVGLC_HSVBC	475-480			PVMSA_HPBVP	185-202
		PVGLC_HSVE4	444-459			PVMSA_HPBVR	185-202
		PVGLC_HSEB	427-442			PVMSA_HPBVS	11-94
		PVGLC_PRVIF	446-461			PVMSA_HPBVW	174-191
		PVGLC_VZVD	150-166			PVMSA_HPBVY	174-191
		PVGLC_VZVS	150-166			PVMSA_HPBVZ	174-191
		PVGLD_HSV11	78-84			PVMT2_IANIN	25-42
		PVGLD_HSV2	79-84			PVMT2_IABAN	25-42
		PVGLE_PVRRI	3-84			PVMT2_IAFOW	25-42
		PVGILF_BR5VA	205-221	265-280		PVMT2_IAPFR	25-42
		PVGILF_BR5VC	205-221	265-280		PVMT2_IAPFW	25-42
		PVGILF_BR5VR	205-221	265-280		PVMT2_IAL1	25-42
		PVGILF_CDVO	388-414			PVMT2_IAL2	25-42
		PVGILF_HRSV1	205-221	265-280		PVMT2_IAMAN	25-42
		PVGILF_HR8VA	205-221	265-280		PVMT2_IAPUE	25-42
		PVGILF_HRSVL	205-221	265-280		PVMT2_IASIN	25-42
		PVGILF_HRSVR	205-221	265-280		PVMT2_IAUDO	25-42
		PVGILF_MEASE	286-302			PVMT2_IAWIL	25-42
		PVGILF_MEASI	289-305				
		PVGILF_MEASY	286-302				
		PVGILF_MUMPM	276-282				
		PVGILF_MUMPR	276-282				
		PVGILF_MUMPS	5-84	276-282			
		PVGILF_NDVA	273-289				
		PVGILF_NDV8	273-289				
		PVGILF_NDVM	273-289				
		PVGILF_NDVT	273-289				
		PVGILF_NDV7G	273-289				
		PVGILF_NDVU	273-289				
		PVGILF_PHODV	268-285	367-383			

	PVGLF_RINDK	282-288							
	PVGLF_RINDL	282-288							
	PVGLF_TRTV	176-191							
	PVGLI_VZVD	278-283							
	PVGLM_HANTB	365-371	900-915						
	PVGLM_HANTH	499-515							
	PVGLM_HANTL	499-515							
	PVGLM_HANTV	499-515							
	PVGLM_PTPV	743-758							
	PVGLM_PUIMH	509-525							
	PVGLM_PUJMS	509-525							
	PVGLM_SEOUR	355-371	901-918						
	PVGLM_SEOUS	355-371	900-915						
	PVGLM_UUK	826-842							
	PVGLP_BEV	889-885							
	PVGLY_LASSG	12-84	426-441						
	PVGLY_LASSJ	12-84	427-442						
	PVGLY_LYCVA	12-84							
	PVGLY_LYCVW	12-84							
	PVGLY_MOFEL	12-84	425-440						
	PVGLY_PIARV	12-84							
	PVGNM_CPMV	1021-1037							
	PVM3_REOVD	521-538							
	PVMAT_MUMPS	191-207							
	PVMAT_NDVA	135-151							
	PVMAT_NDV8	135-151							
	PVMAT_P12HT	189-205							
	PVMAT_SV41	189-205							
	PVMAT_SV5	98-114	132-148						
	PVMP_CAMVC	118-134							
	PVMP_CAMVD	118-134							
	PVMP_CAMVE	118-134							
	PVMP_CAMVN	118-134							
	PVMP_CAMVS	118-134							
	PVMP_CAMVW	118-134							
	PVMP_FMVD	116-131							
	PVMSA_HPBGS	380-385							
	PVMSA_HPBVS	187-202							
	PVMSA_WHV1	376-393							
	PVMSA_WHV59	383-388							
	PVMSA_WHV7	383-388							
	PVMSA_WHV8	383-388							
	PVMSA_WHV81	383-388							
	PVMSA_WHVW8	234-249							
	PVMT2_JAANN	25-40							
	PVMT2_IABAN	25-40							
	PVMT2_IAFOW	25-40							

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**TABLE VII**

**Search Results Summary for P3CTLZIP, P4CTLZIP,  
P5CTLZIP, and P6CTLZIP Motifs**

P3CTLZIP	P4CTLZIP	P5CTLZIP	P6CTLZIP	P8CTLZIP		
LIBRARY FILE	LIBRARY FILE	LIBRARY FILE	LIBRARY FILE	LIBRARY FILE		
PENV BIV27	PENV1 FRSFV	380-388	380-400	PENV BIV06	47-86	625-646
PENV CAEVC	PENV AVISU	88-117	380-400	PENV BIV27	47-86	147-168
PENV CAEVC	PENV BIV27	147-168	170-190	PENV BIV27	225-246	830-851
PENV HV28E	PENV HV12H	123-142	781-801	PENV FLV06	624-645	
PENV HV2D1	PENV HV2D2	8-29	779-798	PENV FLVGL	447-468	605-626
PENV HV2G1	PENV HV28E	778-787	780-800	PENV FLVLB	487-488	825-846
PENV HV2NZ	PENV JSRV	541-560	9-29	PENV FLVSA	444-465	602-623
PENV HV2RO	PENV RSVP	533-552	265-275	PENV FOAMV	153-174	957-878
PENV HV2SB	PHEMA VACCC	173-192	9-29	PENV FSVGA	487-488	825-846
PENV HV2ST	PHEMA VACCI	173-192	428-448	PENV FSVGB	447-468	605-626
PENV JSRV	PHEMA VACCT	173-192	760-770	PENV FSVSM	450-471	608-829
PHEMA P12H	PHEMA VACCV	173-192	400-420	PENV FSVST	487-488	
PHEMA P12HT	PENV BEV	62-81	643-683	PENV GALV	52-73	519-540
PHEMA SV41	PENV MCV1	61-80	643-683	PENV HV2BE	750-771	
PENV THQV	PENV MCV2	61-80	75-86	PENV HV2G1	741-782	
PVG16 BPP22	PVFUS ORNZ	28-48	42-62	PENV HV2NZ	742-763	
PVG24 BPT4	PVG01 HSVB	169-188	924-944	PENV HV2RO	751-772	
PVG36 HSVSA	PVG01 VACCC	378-395	921-941	PENV HV2ST	745-786	
PVG40 HSVI1	PVG01 VACCV	315-334	786-788	PENV MCFE	800-821	
PVG50 HSVSA	PVG01 VARV	378-395	765-785	PENV MCFE3	801-822	
PVG51 BPT4	PVG08 BPT4	627-848	764-784	PENV MLVAV	630-861	
PVG51 HSVI1	PVG10 HSVI1	35-54	789-788	PENV MLVCB	825-846	
PVG66 HSVI1	PVG11 HSVI1	103-122	773-793	PENV MLVFE	639-860	
PVGFI1 BVB	PVG11 BPH2	31-50	493-513	PENV MLVFF	638-860	
PVG12 CVH22	PVG1 SPV1R	669-878	391-411	PENV MLVFP	839-880	
PVG12 BVB	PVG20 BPT4	231-250	391-411	PENV MLVHO	826-847	
PVG12 BVB	PVG32 VZVD	90-109	391-411	PENV MLVKI	167-188	
PVG12 BVD2	PVG36 BPK3	132-151	391-411	PENV MLVMO	829-850	
PVG12 BVK	PVG37 BPT2	19-38	402-422	PENV MLVRD	624-845	
PVG12 BVM	PVG37 BPT4	18-38	81-101	PENV MLVRK	624-845	
PVG1B HSVB1	PVG39 HSVI1	1038-1057	81-101	PENV MSVFB	170-191	
PVG1B HSVBC	PVG41 HSVI1	62-81	397-417	PENV RMCFV	603-824	
PVG1B HSVSA	PVG43 BPPF3	380-399	397-417	PENV SFV1	857-878	
PVG1B LTV8	PVG46 BPPF1	337-356	397-417	PENV SFV3L	157-178	854-876
PVG1B LTV9	PVG59 HSVI1	142-161	493-513	PENV SIV1	437-458	
PVG1B LTVT	PVG81 HSVI1	117-136	322-342	PENV SIVAG	442-483	
PVG1C VZVD	PVG67 HSVI1	318-337	13-33	PENV SIVAI	421-442	
PVG1C VZVS	PVGFI1 BVB	1587-1806	13-33	PENV SIVAT	435-458	
PVG1F P13H4	PVG12 CVBF	991-1010	497-517	PENV SMSAV	42-83	
PVG1H HSVB3	PVG12 CVBL8	981-1010	322-342	PHEMA CVMA5	402-423	
PVG1H HSVB4	PVG12 CVBLY	991-1010	322-342	PHEMA IADE1	286-287	
PVG1H HSVB	PVG12 CVBVM	991-1010	322-342	PHEMA MUMPM	225-246	
PVG1I HSVI1	PVG12 CVBQ	991-1010	322-342	PHEMA MUMPR	225-246	
PVG1M BPMV	PVG12 CVBV	991-1010	322-342	PHEMA MUMPS	225-246	
PVM01 VACCC	PVG12 CVH22	768-787	27-47	PHEMA PHODV	213-234	

PVMO1_VACCV	83-101	128-144	PVGL2_CVMA4	989-1018	PVENV_THQGV	356-376	PIEMA_P12H	13-34	
PVM1_REOVD	227-245		PVGL2_CVMA5	947-968	PVG01_VACCC	288-318	PIEMA_P12HT	13-34	
PVM1_REOVL	227-245		PVGL2_CVMJH	858-877	PVG01_VACCV	288-317	PIEMA_SV5	7-28	378-400
PVMAT_HRSVA	44-62		PVGL2_CVPPF	64-83	PVG01_VACCV	288-318	PIEMA_SV5CM	7-28	378-400
PVMAT_NDVA	180-208		PVGL2_CVPPU	64-83	PVG06_VACCC	31-51	PIEMA_SV5CP	7-28	378-400
PVMAT_NDVB	180-208		PVGL2_CVPR8	814-833	PVG06_VARV	31-51	PIEMA_SV6LN	7-28	378-400
PVMP_CAMVC	183-201		PVGL2_CVPRM	814-833	PVG08_BPPF1	25-45	PVG01_HSVB	189-190	
PVMP_CAMVD	183-201		PVGL2_FIPV	1041-1080	PVG12_HSV11	151-171	PVG01_HSV11	588-610	
PVMP_CAMVE	183-201		PVGL2_IBV8	588-607	PVG22_HSV11	300-320	PVG23_HSV11	314-335	
PVMP_CAMVN	183-201		PVGL2_IBVB	587-608	PVG38_HSV11	648-668	PVG37_BPOX2	65-88	
PVMP_CAMVS	183-201		PVGL2_IBVD2	588-607	PVG51_HSV11	29-49	PVG43_HSV11	157-178	
PVMP_CAMVW	183-201		PVGL2_IBVK	587-608	PVG63_HSV11	338-358	PVG55_HSV11	288-309	
PVMP_FIMVD	180-198		PVGL2_IBVM	587-608	PVG65_HSV11	117-137	PVG55_HSVSA	85-106	
			PVGLB_HCMVA	706-725	PVG74_HSVSA	124-144	PVG56_HSV11	1155-1178	
			PVGLB_HCMVT	707-728	PVGL2_IBV8	328-348	PVG58_HSVSA	288-287	
			PVGLB_HSV8U	117-138	PVGL2_IBVB	327-347	PVG60_HSV11	30-51	
			PVGLB_ILTV8	268-276	PVGL2_IBVD2	328-348	PVG63_HSV11	238-269	
			PVGLB_ILTV8	268-285	PVGL2_IBVD3	328-348	PVG61_IBVB	1858-1877	
			PVGLB_ILTVT	268-285	PVGL2_IBVK	327-347	PVG63_HCMVA	157-178	
			PVGLC_HSV11	3-84	PVGL2_IBVM	327-347	PVGL2_CVBF	1259-1280	
			PVGLC_HSV1K	3-84	PVGL2_IBVJ2	310-330	PVGL2_CVBL9	1259-1280	
			PVGLC_HSVBC	475-494	PVGLB_EBV	732-752	PVGL2_CVBL9	1259-1280	
			PVGLC_CHAV	438-455	PVGLB_HCMVA	750-770	PVGL2_CVBM	1259-1280	
			PVGLG_RABVH	372-381	PVGLB_HCMVT	751-771	PVGL2_CVBQ	1259-1280	
			PVGLI_HSVB	44-63	PVGLB_HSV23	78-89	PVGL2_CVBV	1259-1280	
			PVGLI_VZVD	278-287	PVGLB_HSV2H	78-89	PVGL2_CVM4	1317-1338	
			PVGLM_BUNGE	117-138	PVGLB_HSV29	65-85	PVGL2_CVMA6	1265-1286	
			PVGLM_PHV	152-171	PVGLB_HSV8U	72-82	PVGL2_CVMJH	1178-1197	
			PVGLM_PTPV	987-1018	PVGLB_HSVB2	279-299	PVGLB_HSV11	83-104	
			PVGLM_PUJMH	155-174	PVGLB_HSVBA	63-83	PVGLB_HSV1F	82-103	
			PVGLM_PUJMS	155-174	PVGLB_MCMV8	738-758	PVGLB_HSV1K	82-103	
			PVGLM_RVAV	830-849	PVGLF_P13H4	283-303	PVGLB_HSV1P	83-104	
			PVGLM_RVAVZ	830-849	PVGLG_RABVE	454-474	PVGLB_MCMV8	135-156	
			PVGLM_UJK	655-674	PVGLG_RABVH	454-474	PVGLC_PRVIF	448-467	
			PVGLY_LYCVW	89-108	PVGLG_RABVP	454-474	PVGLF_CDVO	338-357	
			PVGNB_CPMV	1165-1184	PVGLG_RABVS	454-474	PVGLF_MEASE	224-245	
			PVM3_REOVD	521-540	PVGLG_RABVT	454-474	PVGLF_MEASI	227-248	
			PVME1_CVBM	171-180	PVGLH_MCMV8	670-690	PVGLF_MEASY	224-245	
			PVME1_CVH22	138-155	PVGLM_BUNL7	1325-1345	PVGLF_MUNPM	448-467	
			PVME1_CVPPF	174-183	PVGLM_BUNSH	1326-1345	PVGLF_MUNPR	448-467	
			PVME1_CVPPU	174-183	PVGLM_BUNYW	898-1018	PVGLF_MUNPS	448-467	
			PVME1_CVPRM	174-183	PVGLM_HANTH	988-1018	PVGLF_PHODV	305-328	
			PVME1_CVTKC	171-180	PVGLM_HANTH	1000-1020	PVGLF_P1HC	458-477	
					PVGLM_HANTL	1001-1021	PVGLF_P1ZH	450-471	
					PVGLM_HANTV	1001-1021	PVGLF_P1ZH	450-471	
					PVGLM_RVAVZ	1158-1178	PVGLF_P12HT	450-471	
					PVGLM_SEOUR	1000-1020	PVGLF_P13B	405-428	453-474

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**TABLE VIII**

Search Results Summary for P7CTLZIP,  
P8CTLZIP, and P9CTLZIP Motifs

P7CTLZIP		P8CTLZIP		P8CTLZIP			
LIBRARY FILE		LIBRARY FILE		LIBRARY FILE			
PENV BAEVM	202-224	PENV1 FRSFV	380-403	PENV BLVAF		303-327	
PENV HV1B1	488-520	PENV2 FRSFV	380-403	PENV BLVAU		303-327	
PENV HV1B8	483-516	PENV BIV08	178-201	PENV BLVAV		303-327	
PENV HV1B9	484-518	PENV BIV27	207-230	PENV BLVB2		303-327	
PENV HV1BR	503-525	PENV FOAMV	804-887	PENV BLVB6		303-327	
PENV HV1EL	485-517	PENV HV123	176-188	PENV BLVJ		303-327	
PENV HV1H2	488-520	PENV HV2BE	3-26	PENV FIVPE	781-804	781-805	
PENV HV1H3	488-520	PENV HV2CA	760-773	PENV FIVSD		778-803	
PENV HV1J3	510-532	PENV HV2D1	3-26	PENV FIVT2	772-795	780-804	
PENV HV1JR	480-512	PENV HV2G1	772-795	PHEMA CVBLY		391-415	
PENV HV1KB	504-528	PENV HV2NZ	777-800	PHEMA CVBM		391-415	
PENV HV1MA	500-522	PENV JSRV	541-564	PHEMA CVBQ		391-415	
PENV HV1MF	488-518	PENV SFV1	864-887	PHEMA CVHOC		391-415	
PENV HV1ND	488-510	PENV SFV3L	881-884	PHEMA INCCA		442-466	
PENV HV1PV	488-520	PENV SIMM1	803-828	PHEMA INCEN		430-454	
PENV HV1S1	488-511	PENV SIMNK	802-825	PHEMA INCGL		430-454	
PENV HV1Z2	123-146	PENV SIMML	801-824	PHEMA INCY		429-453	
PENV HV1Z8	487-519	PENV SIN54	808-829	PHEMA INCJH		443-487	
PENV HV1Z8	505-527	PENV SIN5P	810-833	PHEMA INCKY		429-453	
PENV HV1ZH	488-520	PHEMA QDVO	200-223	PHEMA INCM1		429-453	
PENV JSRV	378-388	PHEMA PIZH	85-88	PHEMA INCNA		429-453	
PENV MPMV	213-235	PHEMA PIZHT	65-88	PHEMA INCP1		430-454	
PENV SRV1	213-235	PVF11 VACCC	161-184	PHEMA INCP2		430-454	
PHEMA IAAIC	37-59	PVF15 VACCC	25-48	PHEMA INCP3		430-454	
PHEMA IABAN	21-43	PVF15 VACCP	3-26	PHEMA INCTA		430-454	
PHEMA IADA3	37-59	PVG1L AMEPV	313-336	PHEMA INCYA		430-454	
PHEMA IADH2	21-43	PVG28 HSVI1	491-514	PHEMA MUMPM		101-125	
PHEMA IADH3	21-43	PVG43 HSVI1	322-345	PHEMA MUMPR		101-125	
PHEMA IADH4	21-43	PVG52 HSVI1	228-252	PHEMA MUMPS		101-125	
PHEMA IADH5	21-43	PVG67 HSVI1	722-745	PHEMA PITHW		29-53	
PHEMA IADH6	21-43	PVGL2 CVBF	10-33	PENV BEV		62-86	
PHEMA IADH7	21-43	PVGL2 CVBL8	651-674	PVF05 VACCC		280-304	
PHEMA IADM2	37-59	PVGL2 CVBLY	10-33	PVF05 VACCP		280-304	
PHEMA IADMA	28-50	PVGL2 CVM4	1287-1290	PVF05 VACCV		281-305	
PHEMA IADU3	37-59	PVGL2 CVM45	1216-1238	PVF08 VACCC		176-200	
PHEMA IAE6	21-43	PVGL2 CVMJH	1128-1149	PVF09 VACCV		178-200	
PHEMA IAE7	37-59	PVGL2 CVPFS	1274-1287	PVG01 VZVD		58-82	
PHEMA IAMAO	37-59	PVGL2 CVPPU	1272-1285	PVG10 HSVSA		355-378	
PHEMA IAME1	37-59	PVGL2 CVPR8	1050-1073	PVG12 HSVSA		68-82	
PHEMA IAME2	37-59	PVGL2 CVPRM	1050-1073	PVG18 HSVI1		88-112	
PHEMA IAME8	21-43	PVGL2 FIPV	1277-1300	PVG28 HSVI1		173-187	
PHEMA IANT6	37-59	PVGL2 IBV6	196-219	PVG43 HSVI1		108-133	
PHEMA IAU7	21-43	PVGL2 IBV8	195-218	PVG87 HSVI1		108-132	1005-1029
PHEMA IATKM	33-55	PVGL2 IBVD2	196-219	PVG72 HSVI1		720-744	
PHEMA IAUO	37-59	PVGL2 IBVD3	196-219	PVG71 IBVB		3601-3625	

PHEMA_IJV7	39-60	PVGL2_IBVK	185-218	PVGLB_HSVMD	599-613			
PHEMA_IAX31	37-59	PVGL2_IBVM	195-218	PVGLB_ILTV6	597-621			
PHEMA_IAXCO	37-59	PVGL2_IBVU1	178-201	PVGLB_ILTVS	607-631			
PHEMA_IAXH2	21-43	PVGL2_IBVU2	178-201	PVGLB_ILTVT	607-631			
PHEMA_IAXH3	21-43	PVGL2_IBVU3	178-201	PVGLB_HSV11	413-437			
PHEMA_IAXUK	37-59	PVGLB_HCMVA	535-559	PVGLB_VZVD	489-493			
PHEMA_PHODV	36-58	PVGLB_HCMVT	535-559	PVGLF_SV6	401-425			
PHEMA_PIGH	65-87	PVGLB_HSV6A	483-506	PVGLH_HCMVA	574-598			
PHEMA_PIGH	65-87	PVGLB_HCMVS	508-589	PVGLH_HCMVT	573-597			
PVFP7_CAPVK	89-111	PVGLC_HSV11	487-490	PVGLH_HSV11	443-467	803-827		
PVFUS_VACC6	72-84	PVGLC_HSV1K	487-490	PVGLH_HSV1E	443-467	803-827		
PVG01_HSV11	317-339	PVGLC_HSV2	435-458	PVGLM_BUNL7	31-55			
PVG03_VACCC	50-72	PVGLC_HSV23	435-458	PVGLM_BUNSH	31-55			
PVG03_VARV	50-72	PVGLM_BUNL7	1387-1410	PVGLM_HANTH	694-718			
PVG04_VACCC	11-33	PVGLM_BUNSH	1387-1410	PVGLM_RVTV	344-368			
PVG04_VARV	11-33	PVGLM_UUK	988-989	PVGLM_RVTVZ	344-368			
PVG18_HSV11	88-110	PVGLY_JUNIN	12-35	PVGLM_UUK	591-595			
PVG28_HSV11	173-195	PVGLY_LASSG	12-35	PVGNM_CPMV	311-335			
PVG28_HSV11	20-42	PVGLY_LASSJ	12-35	PVGP2_EBV	657-681			
PVG46_HSV11	134-156	PVGLY_LVCVA	12-35	PVGP3_EBV	854-878			
PVG48_HSV5A	71-93	PVGLY_LVCVW	12-35	PVM1_REOVD	280-304			
PVG58_HSV5A	288-288	PVGLY_MPEI	12-35	PVM1_REOVL	280-304			
PVG58_HSV11	287-289	PVGLY_TACV	12-35	PVM21_REOVD	168-192			
PVG5_SPV4	42-64	PVGLY_TACV6	12-35	PVM22_REOVD	168-192			
PVG60_HSV11	53-75	PVGLY_TACV7	12-35	PVM2_REOVL	168-192			
PVG65_HSV11	1347-1369	PVGLY_TACVT	12-35	PVM2_REOVL	168-192			
PVG6_SPV1R	60-82	PVGNM_CPMV	741-764	PVMAT_MEASI	87-111			
PVGL2_IBV6	1058-1078	PVM1_REOVD	324-347	PVMAT_SSPVB	314-338			
PVGL2_IBV8	1055-1077	PVM1_REOVL	454-477	PVME1_CVBM	137-161			
PVGL2_IBVD2	1058-1078	PVMAT_MUMPS	227-250	PVME1_CVHOC	137-161			
PVGL2_IBVK	1055-1077	PVMSA_HPBDB	288-292	PVME1_CVTKE	137-161			
PVGL2_IBVM	1055-1077	PVMSA_HPBDC	288-291	PVME1_IBV6	74-98			
PVGLB_HSV8U	117-139	PVMSA_HPBDC	231-254	PVME1_IBV8	74-98			
PVGLB_HSVB2	745-787	PVMSA_HPBDC	288-292	PVME1_IBVB2	74-98			
PVGLC_HSVMB	389-421	PVMSA_HPBHE	238-259	PVME1_IBVK	74-98			
PVGLC_HSVMB	389-420			PVMSA_HPBGS	271-295			
PVGLC_HSVMM	389-421			PVMSA_WHV1	269-293			
PVGLF_BR5VA	265-287	482-504		PVMSA_WHV59	274-298			
PVGLF_BR5VC	484-508			PVMSA_WHV7	274-288			
PVGLF_BR5VR	484-508			PVMSA_WHV8	274-288			
PVGLF_HRSV1	484-508			PVMSA_WHV8I	274-298			
PVGLF_HRSVA	484-508			PVMSA_WHVW6	125-149			
PVGLF_HRSVL	484-508							
PVGLF_HRSVR	484-508							
PVGLF_HRSV1	452-474							
PVGLG_IHNV	77-89							
PVGLG_VHSVO	406-428							

[illegible]

## TABLE IX

### Search Results Summary for P12CTLZIP Motif

[illegible]

PENV HV1ZH	123-142	438-453	498-520							
PENV HV2BE	3-26	750-776	781-804							
PENV HV2CA	760-777									
PENV HV2D1	3-26	741-768	772-796							
PENV HV2D2	9-28									
PENV HV2G1	741-768	772-796								
PENV HV2NZ	742-767	777-800								
PENV HV2RO	751-776									
PENV HV2S8	743-768	778-804								
PENV HV2ST	745-770									
PENV JSRV	104-119	289-325	376-398	541-564						
PENV MCFF	800-821									
PENV MCFE3	801-822									
PENV MLVAV	830-861									
PENV MLVCB	826-848									
PENV MLVF5	838-880									
PENV MLVFF	839-880									
PENV MLVFP	839-880									
PENV MLVHO	826-847									
PENV MLVKI	167-188									
PENV MLVMO	828-860									
PENV MLVRD	824-845									
PENV MLVRK	824-845									
PENV MMTVB	843-863									
PENV MMTVG	843-863									
PENV MPMV	213-235									
PENV MSVFB	170-191									
PENV OMVVS	75-100	658-693								
PENV RMCVV	803-824									
PENV RSVP	42-88	533-552								
PENV SFV1	300-325	710-727	864-887	924-951	957-978					
PENV SFV3L	157-178	304-328	707-724	861-884	921-948	954-976				
PENV SIVA1	437-458									
PENV SIVAG	442-483									
PENV SIVAI	421-442									
PENV SIVAT	435-456									
PENV SIVGB	93-108									
PENV SIVM1	766-783	803-828								
PENV SIVM2	138-154	786-792	802-826							
PENV SIVMK	138-154	784-791	801-824							
PENV SIVML	789-798	806-828								
PENV SIVS4	773-793	810-833								
PENV SMSAV	42-83									
PENV SRV1	213-235									
PHEMA CDVO	36-53	200-223								
PHEMA CVBLY	391-415									
PHEMA CVRM	391-415									

[illegible]



[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

PVGLM PTPV	743-766	997-1016	1276-1302						
PVGLM PUUMH	155-174	509-525	712-728						
PVGLM PUUMS	155-174	509-525	712-729	1092-1117					
PVGLM RVFV	53-80	344-368	830-856						
PVGLM RVFV2	53-80	344-368	830-856	1156-1179					
PVGLM SEOUR	355-371	693-718	901-916	1000-1020					
PVGLM SEOUS	355-371	692-717	800-916	999-1019					
PVGLM UUK	561-585	655-674	826-842	925-952	986-989				
PVGLP BEV	430-452	869-885	1099-1124	1546-1558					
PVGLX_PVRRI	149-176								
PVGLY JUNIN	12-38								
PVGLY LASSG	12-38	237-258	426-448						
PVGLY LASSJ	12-38	236-259	427-449						
PVGLY LYCVA	12-38								
PVGLY LYCVW	12-38	89-108							
PVGLY MOPEI	12-38	425-447							
PVGLY PIARV	12-38	441-466							
PVGLY TACV	12-38								
PVGLY TACV5	12-38								
PVGLY TACV7	12-38								
PVGLY TACVT	12-38								
PVGNB CPMV	141-161	588-594	757-783	1110-1135	1165-1184				
PVGNM BPMV	678-696								
PVGNM CPMV	311-335	741-764	1021-1037						
PVGP2 EBV	667-681								
PVGP3 EBV	854-878								
PVGP8 EBV	67-86								
PVM01_VACCC	134-159	177-195	281-302						
PVM01_VACCV	83-108	126-144	230-251						
PVM1_REOVD	141-168	227-245	280-304	324-347	414-438	454-477			
PVM1_REOVL	141-168	227-245	280-304	414-436	454-477				
PVM21_REOVD	168-192								
PVM22_REOVD	168-192								
PVM2_REOVJ	168-192								
PVM2_REOVL	168-192								
PVM3_REOVD	304-326	521-540							
PVMAT_BR9VA	37-62								
PVMAT_CDVO	148-165	293-309							
PVMAT_HRSVA	44-62	139-160							
PVMAT_LPMV	311-338								
PVMAT_MEASE	293-309								
PVMAT_MEASH	293-309								
PVMAT_MEASJ	87-111								
PVMAT_MEASU	293-309								
PVMAT_MUMPS	191-207	227-250	310-330						
PVMAT_NDVA	135-151	190-208	308-329						
PVMAT_NDVB	135-151	190-208	308-329						



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## TABLE X

### Search Results Summary for P23CTLZIP Motif

P23LZIPC					
LIBRARY FILE					
PENV AVISU	98-136				
PENV BAEVM	202-240	528-554			
PENV BIV06	434-472	526-553	628-659		
PENV BIV27	554-582	657-688			
PENV CAEVG	44-78				
PENV EIAV1	785-828				
PENV EIAV2	785-828				
PENV EIAV3	785-828				
PENV EIAV5	785-828				
PENV EIAV8	785-828				
PENV EIAVC	785-828				
PENV EIAVW	785-828				
PENV EIAVY	785-828				
PENV FIVPE	128-168				
PENV FIVT2	46-74				
PENV FLVGL	447-475				
PENV FLVLB	487-495				
PENV FLVBA	444-472				
PENV FOAMV	44-78	481-519	552-584		
PENV FRSPB	315-350				
PENV FSVGA	467-495				
PENV FSVGB	447-475				
PENV FSVSM	460-478				
PENV FSVBT	487-495				
PENV GALV	519-554				
PENV HV1A2	728-782				
PENV HV1B1	730-783				
PENV HV1B8	725-758				
PENV HV1BN	743-781				
PENV HV1BR	735-768				
PENV HV1C4	742-775				
PENV HV1EL	254-285	727-760			
PENV HV1H2	730-783				
PENV HV1H3	730-783				
PENV HV1J3	741-774				
PENV HV1JR	722-755				
PENV HV1KB	552-588	762-790			
PENV HV1MA	258-288	733-768			
PENV HV1MF	728-781				
PENV HV1MN	382-430	731-764			
PENV HV1ND	248-278				
PENV HV1OY	729-782				
PENV HV1PV	730-763				
PENV HV1RH	739-772				
PENV HV1SC	730-783				

PENV HV1W1	730-783				
PENV HV1W2	721-764				
PENV HV1Z2	264-285	727-760			
PENV HV1Z3	250-281				
PENV HV1Z8	265-288	728-782			
PENV HV1Z8	285-288				
PENV HV2BE	781-811				
PENV HV2D1	772-802				
PENV HV2G1	772-802				
PENV HV2NZ	777-814				
PENV HV2S8	743-776				
PENV JSRV	288-332	484-515			
PENV MMTVB	435-472				
PENV MMTVG	435-472				
PENV RSP	533-570				
PENV SFV1	44-78	482-530			
PENV SFV3L	48-82	550-588			
PENV SIVCZ	745-778				
PENV SIVGB	247-277	353-388			
PENV SIVM1	788-800				
PENV SIVMK	785-789				
PENV SIVML	511-545	784-788			
PENV SIVS4	458-488				
PENV SIVSP	482-480	810-840			
PHEMA CDVO	200-234				
PHEMA IABUD	23-55				
PHEMA IACKA	23-55				
PHEMA IACKV	517-547				
PHEMA IADA1	23-55				
PHEMA IADCZ	23-55				
PHEMA IADH5	283-323				
PHEMA IADNZ	23-55				
PHEMA IAFPR	16-51				
PHEMA IAGRE	23-55				
PHEMA IAMAA	22-54				
PHEMA IAMAB	27-58				
PHEMA IARUD	23-55				
PHEMA IASE2	23-55				
PHEMA IASTA	517-547				
PHEMA MUMPM	18-52	101-132			
PHEMA MUMPR	18-52	101-132			
PHEMA MUMPS	18-52	101-132			
PHEMA NDVA	60-88				
PHEMA NDVB	60-88				
PHEMA NDVD	60-88				
PHEMA NDVH	60-88				
PHEMA NDVI	60-88				

PHEMA_NDVM	60-88						
PHEMA_NDVQ	60-88						
PHEMA_NDVTG	60-88						
PHEMA_NDVU	60-88						
PHEMA_PI1HW	28-60	186-233					
PHEMA_PI2H	13-48	334-369					
PHEMA_PI2HT	13-48	334-369					
PHEMA_PI3B	184-231						
PHEMA_PI3H4	184-231						
PHEMA_PI3HA	184-231						
PHEMA_PI3HT	184-231						
PHEMA_PI3HU	184-231						
PHEMA_PI3HV	184-231						
PHEMA_PI3HW	184-231						
PHEMA_PI3HX	184-231						
PHEMA_PI4HA	245-280	338-378					
PHEMA_RACVI	255-283						
PHEMA_RINDL	282-313						
PHEMA_SENDE	18-54	186-233					
PHEMA_SENDF	18-54	186-233					
PHEMA_SENDH	18-54	186-233					
PHEMA_SENDJ	18-54	186-233					
PHEMA_SENDZ	23-54	186-233					
PHEMA_6V41	55-84	330-365					
PHEMA_6V6	7-35						
PHEMA_6V5CM	7-41						
PHEMA_6V5CP	7-41						
PHEMA_6V5LN	7-35						
PHEMA_VACCC	258-284						
PHEMA_VACCI	258-284						
PHEMA_VACCT	258-284						
PHEMA_VACCV	258-284						
PVENV_BEV	18-51	87-117					
PVENV_DHV11	287-335						
PVENV_MCV1	203-238						
PVENV_MCV2	203-238						
PVENV_VACCC	206-241						
PVENV_VACCI	208-241						
PVENV_VACCP	208-241						
PVENV_VACCV	208-241						
PVF03_VACCC	2-40	61-93					
PVF03_VACCV	2-40	61-93					
PVFP1_FOWPV	287-330						
PVFP4_FOWPV	237-287						
PVFP7_CAPVK	88-118						
PVFUS_VACCC	28-61						
PVFUS_VACCV	28-61						

PVG01_HSV11	317-348				
PVG02_HSVB	183-188				
PVG02_VACCV	92-120				
PVG02_VARV	92-120				
PVG03_HSV11	108-138				
PVG06_HSV11	54-83				
PVG08_VACCC	98-138				
PVG08_VARV	98-138				
PVG07_VACCC	113-145				
PVG07_VARV	113-145				
PVG08_VACCC	303-338				
PVG08_VACCV	288-301				
PVG08_VARV	303-338				
PVG11_HSV11	150-183				
PVG12_HSV11	208-243				
PVG12_HSV5A	68-108				
PVG1_SPV1R	254-282	303-337	414-452		
PVG22_HSV11	300-337	847-878			
PVG23_HSV11	70-108				
PVG28_HSV11	84-125				
PVG27_HSV5A	38-74				
PVG28_HSV11	481-521				
PVG28_HSV5A	7-40				
PVG2R_AMEPV	180-217				
PVG2_SPV4	208-244				
PVG35_HSV11	15-48	180-228			
PVG36_HSV5A	151-185				
PVG38_HSV11	543-577	848-882			
PVG40_HSV5A	187-216				
PVG41_HSV11	11-45	202-233			
PVG42_HSV11	91-125				
PVG43_HSV11	108-140	157-185			
PVG48_HSV11	888-925				
PVG48_HSV5A	328-357				
PVG50_HSV5A	113-141				
PVG51_HSV11	28-84	84-120			
PVG52_HSV11	98-134				
PVG55_HSV11	100-129				
PVG56_HSV11	631-687	1081-1128			
PVG58_HSV11	342-376	480-508			
PVG58_HSV5A	25-60	195-233			
PVG58_HSV11	82-118				
PVG61_HSV11	78-108				
PVG64_HSV11	55-89	383-401	420-452		
PVG65_HSV11	801-838	1280-1328			
PVG67_HSV11	150-188	1160-1185			
PVG6_SPV1R	80-89				

PVG71 H8V9A	128-168				
PVG72 HSV11	445-478	720-761	1158-1189	1252-1285	
PVG76 HSV11	283-291	387-422			
PVG78 HSV11	187-221				
PVG7 SPV1R	18-48				
PVGFT IBVB	1719-1747	1856-1891	2108-2146	3601-3633	
PVGH3 HCMVA	80-115	157-185			
PVGL2 CVBF	1259-1294				
PVGL2 CVBL0	851-881	1259-1294			
PVGL2 CVBLY		1259-1284			
PVGL2 CVBM		1259-1294			
PVGL2 CVBQ		1259-1294			
PVGL2 CVBV		1259-1284			
PVGL2 CVH22	1063-1088				
PVGL2 CVM4	1287-1304				
PVGL2 CVMA5	1215-1252				
PVGL2 CVMJH	1128-1163				
PVGL2 CVPF6	832-885	738-784	1328-1363		
PVGL2 CVPPU	830-863	734-782	1328-1361		
PVGL2 CVPR8	512-540	1104-1139			
PVGL2 CVPRM	408-441	1104-1139			
PVGL2 FIPV	835-888	738-787	1331-1368		
PVGL2 IBVB	153-188				
PVGLB HCMVA	116-147	706-743			
PVGLB HCMVT	118-147	707-744			
PVGLB HSV8U	72-110				
PVGLB HSVB1	254-288				
PVGLB HSVB2	284-299	745-774			
PVGLB HSVBC	253-287				
PVGLB ILTV8	442-472				
PVGLB ILTV9	452-482				
PVGLB ILTVT	452-482				
PVGLB MCMV8	135-163	738-776			
PVGLC HSV11	487-500				
PVGLC HSV1K	487-500				
PVGLC HSV2	435-465				
PVGLC HSV23	436-466				
PVGLC HSVBC	475-507				
PVGLC VZVD	351-388	513-548			
PVGLC VZV8	351-388	513-548			
PVGLD HSV8A	340-370				
PVGLD HSV8B	41-70	390-420			
PVGLD HSV8C	41-70	390-420			
PVGLD HSV8D	85-125				
PVGLD HSV8E	63-100	380-420			
PVGLD HSV8F	63-100	382-422			
PVGLD HSV8G	332-369				



PVGLF BRSA	285-301	482-511			
PVGLF BRVC	484-513				
PVGLF BRVR	484-513				
PVGLF CDVO	582-598				
PVGLF HRSV1	484-513				
PVGLF HRSVA	484-513				
PVGLF HRSVL	484-513				
PVGLF HRSVR	484-513				
PVGLF MEASE	224-258	451-484			
PVGLF MEASI	227-258	454-487			
PVGLF MEASY	224-258	451-484			
PVGLF MUMPM	448-474				
PVGLF MUMPR	448-474				
PVGLF MUMPS	5-38	448-474			
PVGLF NDVI	132-165				
PVGLF PHODV	531-585				
PVGLF P11HC	458-484				
PVGLF P13B	453-481				
PVGLF P13H4	453-481				
PVGLF RINDK	220-252	447-480			
PVGLF RINDL	220-252	447-480			
PVGLF SEND5	480-488				
PVGLF SENDF	480-488				
PVGLF SENDH	480-488				
PVGLF SENDJ	480-488				
PVGLF SENDZ	480-488				
PVGLF SV5	448-474				
PVGLF TRTV	452-481				
PVGLG HSEB	327-364				
PVGLG SYN	524-553				
PVGLG VSVIG	450-488				
PVGLG VSVJO	457-492				
PVGLG VSVVO	450-488				
PVGLG VSVSJ	450-488				
PVGLH HCMVA	691-718				
PVGLH HCMVT	680-718				
PVGLH HSBG	640-677				
PVGLH HSE4	814-850				
PVGLH HSEB	807-843				
PVGLI HCMVA	158-184				
PVGLM BUNGE	197-227	438-468	982-1020	1048-1084	
PVGLM BUNL7	180-220				
PVGLM BUNSH	180-220	344-381			
PVGLM BUNYW	183-228	434-472	823-854		
PVGLM DUGBV	244-273	637-672	888-915	935-985	1403-1441
PVGLM HANTB	610-641	1081-1119			
PVGLM HANTH	188-222	612-643	1082-1120		

PVGLM_HANTL	188-222	612-843	1083-1121	
PVGLM_HANTV	188-222	612-843	1083-1121	
PVGLM_PHV	616-848	1088-1121		
PVGLM_PTPV	849-882	1275-1308		
PVGLM_PUUMH	820-853	1092-1125		
PVGLM_PUUMS	620-853	1092-1125		
PVGLM_RVTV	620-853	830-863		
PVGLM_RVTVZ	620-853	830-863	1156-1185	
PVGLM_SEOUR	605-841	1082-1120		
PVGLM_SEOUS	610-841	1081-1118		
PVGLM_UUK	431-468	988-995		
PVGLP_BEV	1481-1528			
PVGLY_JUNIN	12-45			
PVGLY_LASSG	237-285			
PVGLY_LASSJ	238-288			
PVGLY_PIARV	12-50			
PVGLY_TACV	12-50			
PVGLY_TACV6	12-50	88-124		
PVGLY_TACV7	12-50	88-124		
PVGLY_TACVT	12-50	88-124		
PVGNB_CPMV	1527-1555			
PVGNM_8PMV	137-167	280-327	837-868	
PVGNM_CPMV	209-242	741-771		
PVGNM_CPSMV	50-88	478-515		
PVGNM_RCMV	766-798			
PVGP2_EBV	78-111			
PVGP3_EBV	78-111			
PVM1_REOVD	280-318	324-361		
PVM1_REOVL	280-318			
PVM21_REOVD	168-188			
PVM22_REOVD	168-188			
PVM2_REOVL	168-188			
PVM2_REOVL	168-188			
PVM3_REOVD	333-384			
PVMAT_SV5	308-342			
PVMAT_TRTV	122-150			
PVME1_CVBM	64-102			
PVME1_CVHOC	64-102			
PVME1_CVMA5	65-103			
PVME1_CVMJH	65-103			
PVME1_CVTKC	64-102			
PVME1_EBV	178-213			
PVMP_CERV	93-128			
PVMP_SOCMV	66-98	273-303		
PVMSA_HPBDB	201-238	268-302		
PVMSA_HPBDC	184-227	268-301		
PVMSA_HPBDO	157-190	231-264		

[illegible]

### 5.3. SYNTHESIS OF PEPTIDES

The peptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman and Co., NY, 5 which is incorporated herein by reference in its entirety. Short peptides, for example, can be synthesized on a solid support or in solution. Longer peptides may be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the peptides 10 of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, *Molecular Cloning*, A Laboratory Manual, Vols. 1-3, Cold Spring Harbor 15 Press, NY.

The peptides of the invention may alternatively be synthesized such that one or more of the bonds which link the amino acid residues of the peptides are non-peptide bonds. These alternative non-peptide 20 bonds may be formed by utilizing reactions well known to those in the art, and may include, but are not limited to imino, ester, hydrazide, semicarbazide, and azo bonds, to name but a few. In yet another embodiment of the invention, peptides comprising the 25 sequences described above may be synthesized with additional chemical groups present at their amino and/or carboxy termini, such that, for example, the stability, bioavailability, and/or inhibitory activity of the peptides is enhanced. For example, hydrophobic 30 groups such as carbobenzoxy, dansyl, or t-butyloxycarbonyl groups, may be added to the peptides' amino termini. Likewise, an acetyl group or a 9-fluorenylmethoxy-carbonyl group may be placed at the peptides' amino termini. (See "X" in Tables I to IV, 35 above.) Additionally, the hydrophobic group, t-

butyloxycarbonyl, or an amido group may be added to the peptides' carboxy termini. (See "Z" in Tables I to IV, above.) Further, the peptides of the invention may be synthesized such that their steric configuration is altered. For example, the D-isomer of one or more of the amino acid residues of the peptide may be used, rather than the usual L-isomer. Still further, at least one of the amino acid residues of the peptides of the invention may be substituted by one of the well known non-naturally occurring amino acid residues. Alterations such as these may serve to increase the stability, bioavailability and/or inhibitory action of the peptides of the invention.

Any of the peptides described above may, additionally, have a non-peptide macromolecular carrier group covalently attached to their amino and/or carboxy termini. Such macromolecular carrier groups may include, for example, lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates. "X", in Tables I to IV, above, may therefore additionally represent any of the above macromolecular carrier groups covalently attached to the amino terminus of a peptide. Likewise, "Z", in Tables I to IV, may additionally represent any of the macromolecular carrier groups described above.

#### 5.4. ASSAYS FOR ANTIVIRAL ACTIVITY

The antiviral activity exhibited by the peptides of the invention may be measured, for example, by easily performed in vitro assays, such as those described below, which can test the peptides' ability to inhibit syncytia formation, or their ability to inhibit infection by cell-free virus. Using these assays, such parameters as the relative antiviral activity of the peptides, exhibit against a given strain of virus and/or the strain specific inhibitory

activity of the peptide can be determined. A cell fusion assay may be utilized to test the peptides' ability to inhibit HIV-induced syncytia formation in vitro. Such an assay may comprise culturing uninfected CD-4<sup>+</sup> cells (such as Molt or CEM cells, for example) in the presence of chronically HIV-infected cells and a peptide to be assayed. For each peptide, a range of peptide concentrations may be tested. This range should include a control culture wherein no peptide has been added. Standard conditions for culturing, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytia formation.

A reverse transcriptase (RT) assay may be utilized to test the peptides' ability to inhibit infection of CD-4<sup>+</sup> cells by cell-free HIV. Such an assay may comprise culturing an appropriate concentration (i.e., TCID<sub>50</sub>) of virus and CD-4<sup>+</sup> cells in the presence of the peptide to be tested. Culture conditions well known to those in the art are used. As above, a range of peptide concentrations may be used, in addition to a control culture wherein no peptide has been added. After incubation for an appropriate period (e.g., 7 days) of culturing, a cell-free supernatant is prepared, using standard procedures, and tested for the presence of RT activity as a measure of successful infection. The RT activity may be tested using standard techniques such as those described by, for example, Goff et al. (Goff, S. et al., 1981, J. Virol. 38:239-248) and/or Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). These references are incorporated herein by reference in their entirety.

Standard methods which are well-known to those of skill in the art may be utilized for assaying non-retroviral activity. See, for example, Pringle et al. (Pringle, C.R. et al., 1985, J. Medical Virology 17:377-386) for a discussion of respiratory syncytial virus and parainfluenza virus activity assay techniques. Further, see, for example, "Zinsser Microbiology", 1988, Joklik, W.K. et al., eds., Appleton & Lange, Norwalk, CT, 19th ed., for a general review of such techniques. These references are incorporated by reference herein in its entirety.

#### 5.5. USES OF THE PEPTIDES OF THE INVENTION

The DP-178 (SEQ ID:1) peptides of the invention, and DP-178 fragments, analogs, and homologs, exhibit potent antiviral activity. The DP-107-like and DP-178-like peptides of the invention preferably exhibit antiviral activity. As such, the peptides may be used as inhibitors of human and non-human viral and retroviral, especially HIV, transmission to uninfected cells.

The human retroviruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to all strains of HIV-1 and HIV-2 and the human T-lymphocyte viruses (HTLV-I and II). The non-human retroviruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency, sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

Non retroviral viruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to human respiratory syncytial virus, canine distemper virus, newcastle disease virus, human parainfluenza virus, and influenza

viruses. Further, any virus or retrovirus containing peptides listed in Tables V through X above, may be inhibited by the peptides of the invention.

As discussed more fully, below, in Section 5.5.1 and in the Example presented, below, in Section 8, DP-107 and DP-178, and DP-107-like and DP-178-like peptides form non-covalent protein-protein interactions which are required for normal activity of the virus. Thus, the peptides of the invention may also be utilized as components in assays for the identification of compounds that interfere with such protein-protein interactions and may, therefore, act as antiviral agents. These assays are discussed, below, in Section 5.5.1.

5.5.1. ANTIVIRAL COMPOUND SCREENING SCREENING  
ASSAYS FOR COMPOUNDS THAT INTERACT WITH  
THE PKD1 GENE PRODUCT

As demonstrated in the Example presented in Section 8, below, DP-107 and DP-178 portions of the TM protein gp41 form non-covalent protein-protein interactions. As also demonstrated, the maintenance of such interactions is necessary for normal viral infectivity. Thus, compounds which bind DP-107, bind DP-178, and/or act to disrupt normal DP-107/DP-178 protein-protein interactions may act as patent antiviral agents. Described below are assays for the identification of such compounds. Note that, while, for ease and clarity of discussion, DP-107 and DP-178 peptides will be used as components of the assays described, but it is to be understood that any of the DP-107-like or DP-178-like peptides described, above, in Sections 5.1 and 5.2 may also be utilized as part of these screens for antiviral compounds.

Compounds which may be tested for an ability to bind DP-107, DP-178, and/or disrupt DP-107/DP-178 interactions, and which therefore, potentially



represent antiviral compounds, include, but are not limited to, peptides made of D- and/or L-configuration amino acids (in, for example, the form of random peptide libraries; see Lam, K.S. et al., 1991, Nature 354:82-84), phosphopeptides (in, for example, the form of random or partially degenerate, directed phosphopeptide libraries; see, for example, Songyang, Z. et al., 1993, Cell 72:767-778), antibodies, and small organic or inorganic molecules. Synthetic compounds, natural products, and other sources of potentially effective materials may be screened in a variety of ways, as described in this Section. The compounds, antibodies, or other molecules identified may be tested for an ability to inhibit viral activity, utilizing, for example, viral assays such as those described, above, in Section 5.4.

Among the peptides which may be tested are soluble peptides comprising DP-107 and/or DP-178 domains, and peptides comprising DP-107 and/or DP-178 domains having one or more mutations within one or both of the domains, such as the M41-P peptide described, below, in the Example presented in Section 8, which contains a isoleucine to proline mutation within the DP-178 sequence.

In one embodiment of such screening methods is a method for identifying a compound to be tested for antiviral ability comprising:

- (a) exposing at least one compound to a peptide comprising a DP-107 peptide for a time sufficient to allow binding of the compound to the DP-107 peptide;
- (b) removing non-bound compounds; and
- (c) determining the presence of the compound bound to the DP-107 peptide, thereby identifying an agent to be tested for antiviral ability.

In a second embodiment of such screening methods is a method for identifying a compound to be tested for antiviral ability comprising:

- 5 (a) exposing at least one compound to a peptide comprising a DP-178 peptide for a time sufficient to allow binding of the compound to the DP-178 peptide;
- (b) removing non-bound compounds; and
- (c) determining the presence of the compound bound to the DP-178 peptide,
- 10 thereby identifying an agent to be tested for antiviral ability.

One method utilizing these types of approaches that may be pursued in the isolation of such DP-107-binding or DP-178-binding compounds is an assay which  
15 would include the attachment of either the DP-107 or the DP-178 peptide to a solid matrix, such as, for example, agarose or plastic beads, microtiter plate wells, petri dishes, or membranes composed of, for example, nylon or nitrocellulose. In such an assay  
20 system, either the DP-107 or DP-178 protein may be anchored onto a solid surface, and the compound, or test substance, which is not anchored, is labeled, either directly or indirectly. In practice, microtiter plates are conveniently utilized. The  
25 anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody, preferably a  
30 monoclonal antibody, specific for the protein may be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the labeled  
35 compound is added to the coated surface containing the anchored DP-107 or DP-178 peptide. After the reaction

is complete, unreacted components are removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways.

5 Where the compound is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the labeled component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using  
10 a labeled antibody specific for the compound (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody).

Alternatively, such an assay can be conducted in a liquid phase, the reaction products separated from  
15 unreacted components, and complexes detected; e.g., using an immobilized antibody specific for DP-107 or DP-178, whichever is appropriate for the given assay, or an antibody specific for the compound, i.e., the test substance, in order to anchor any complexes  
20 formed in solution, and a labeled antibody specific for the other member of the complex to detect anchored complexes.

By utilizing procedures such as this, large numbers of types of molecules may be simultaneously  
25 screened for DP-107 or DP-178-binding capability, and thus potential antiviral activity.

Further, compounds may be screened for an ability to inhibit the formation of or, alternatively, disrupt DP-107/DP-178 complexes. Such compounds may then be  
30 tested for antiviral capability. For ease of description, DP-107 and DP-178 will be referred to as "binding partners." Compounds that disrupt such interactions may exhibit antiviral activity. Such compounds may include, but are not limited to  
35

molecules such as antibodies, peptides, and the like described above.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the DP-107 and DP-178 peptides involves  
5 preparing a reaction mixture containing peptides under conditions and for a time sufficient to allow the two peptides to interact and bind, thus forming a complex. In order to test a compound for disruptive activity, the reaction is conducted in the presence and absence  
10 of the test compound, i.e., the test compound may be initially included in the reaction mixture, or added at a time subsequent to the addition of one of the binding partners; controls are incubated without the test compound or with a placebo. The formation of any  
15 complexes between the binding partners is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound indicates that the compound interferes with the interaction of the DP-107 and  
20 DP-178 peptides.

The assay for compounds that interfere with the interaction of the binding partners can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring one of the  
25 binding partners onto a solid phase and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be  
30 varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the binding partners, e.g., by competition, can be identified by conducting the reaction in the presence  
35 of the test substance; i.e., by adding the test

substance to the reaction mixture prior to or simultaneously with the binding partners. On the other hand, test compounds that disrupt preformed complexes, e.g. compounds with higher binding constants that displace one of the binding partners from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are described briefly below.

5  
10 In a heterogeneous assay system, one binding partner, e.g., either the DP-107 or DP-178 peptide, is anchored onto a solid surface, and its binding partner, which is not anchored, is labeled, either directly or indirectly. In practice, microtiter plates are conveniently utilized. The anchored  
15 species may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody specific for the protein may  
20 be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the binding partner of the immobilized species is added to the coated surface with or without the test compound.  
25 After the reaction is complete, unreacted components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways.  
30 Where the binding partner was pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the binding partner is not pre-labeled, an indirect label can be used to detect complexes anchored on the  
35 surface; e.g., using a labeled antibody specific for

the binding partner (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which inhibit complex formation or which disrupt preformed  
5 complexes can be detected.

Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from unreacted components, and complexes detected; e.g.,  
10 using an immobilized antibody specific for one binding partner to anchor any complexes formed in solution, and a labeled antibody specific for the other binding partner to detect anchored complexes. Again, depending upon the order of addition of reactants to  
15 the liquid phase, test compounds which inhibit complex or which disrupt preformed complexes can be identified.

In an alternate embodiment of the invention, a homogeneous assay can be used. In this approach, a  
20 preformed complex of the DP-107 and DP-178 peptides is prepared in which one of the binding partners is labeled, but the signal generated by the label is quenched due to complex formation (see, e.g., U.S. Patent No. 4,109,496 by Rubenstein which utilizes this  
25 approach for immunoassays). The addition of a test substance that competes with and displaces one of the binding partners from the preformed complex will result in the generation of a signal above background. In this way, test substances which disrupt DP-107/  
30 DP-178 protein-protein interaction can be identified.

#### 5.5 PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

With respect to HIV, the peptides of the  
35 invention may be used as a therapeutic in the

treatment of AIDS. The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's  
5 Pharmaceutical Sciences", 18th ed., 1990, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including  
10 intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. Most preferably, administration is intravenous. For injection, the agents of the invention may be  
15 formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated  
20 are used in the formulation. Such penetrants are generally known in the art.

In addition, the peptides may be used as a prophylactic measure in previously uninfected individuals after acute exposure to an HIV virus.  
25 Examples of such prophylactic use of the peptides may include, but are not limited to, prevention of virus transmission from mother to infant and other settings where the likelihood of HIV transmission exists, such as, for example, accidents in health care settings  
30 wherein workers are exposed to HIV-containing blood products. The peptides of the invention in such cases may serve the role of a prophylactic vaccine, wherein the host raises antibodies against the peptides of the invention, which then serve to neutralize HIV viruses  
35 by, for example, inhibiting further HIV infection.

Administration of the peptides of the invention as a prophylactic vaccine, therefore, would comprise administering to a host a concentration of peptides effective in raising an immune response which is sufficient to neutralize HIV, by, for example,  
5 inhibiting HIV ability to infect cells. The exact concentration will depend upon the specific peptide to be administered, but may be determined by using standard techniques for assaying the development of an immune response which are well known to those of  
10 ordinary skill in the art. The peptides to be used as vaccines are usually administered intramuscularly.

The peptides may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include, but are not  
15 limited to mineral gels such as aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful human adjuvants such as BCG and Corynebacterium parvum. Many methods may  
20 be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

25 Alternatively, an effective concentration of polyclonal or monoclonal antibodies raised against the peptides of the invention may be administered to a host so that no uninfected cells become infected by HIV. The exact concentration of such antibodies will  
30 vary according to each specific antibody preparation, but may be determined using standard techniques well known to those of ordinary skill in the art. Administration of the antibodies may be accomplished using a variety of techniques, including, but not  
35 limited to those described in this section.



Effective dosages of the peptides of the invention to be administered may be determined through procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. Given the data  
5 presented below in Section 6, DP-178, for example, may prove efficacious in vivo at doses required achieve circulating levels of 10ng per ml of peptide.

A therapeutically effective dose refers to that amount of the compound sufficient to result in  
10 amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or  
15 experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and  
20 therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and  
25 animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with  
30 little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the  
35 therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal disruption of the PTK/adaptor

protein complex, or a half-maximal inhibition of the cellular level and/or activity of a complex component) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for  
5 example, by high performance liquid chromatography (HPLC).

The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl  
10 et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ  
15 dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the oncogenic disorder of interest  
20 will vary with the severity of the condition to be treated and to the route of administration. The dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that  
25 discussed above may be used in veterinary medicine.

As demonstrated in the Example presented below in Section 6, the antiviral activity of the peptides of the invention may show a pronounced type and subtype specificity, i.e., specific peptides may be effective  
30 in inhibiting the activity of only specific viruses. This feature of the invention presents many advantages. One such advantage, for example, lies in the field of diagnostics, wherein one can use the antiviral specificity of the peptide of the invention  
35 to ascertain the identity of a viral isolate. With

respect to HIV, one may easily determine whether a viral isolate consists of an HIV-1 or HIV-2 strain. For example, uninfected CD-4<sup>+</sup> cells may be co-infected with an isolate which has been identified as containing HIV the DP-178 (SEQ ID:1) peptide, after  
5 which the retroviral activity of cell supernatants may be assayed, using, for example, the techniques described above in Section 5.2. Those isolates whose retroviral activity is completely or nearly completely inhibited contain HIV-1. Those isolates whose viral  
10 activity is unchanged or only reduced by a small amount, may be considered to not contain HIV-1. Such an isolate may then be treated with one or more of the other DP-178 peptides of the invention, and subsequently be tested for its viral activity in order  
15 to determine the identify of the viral isolate.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the  
20 invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be  
25 formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups,  
30 slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective  
35 amount to achieve its intended purpose. Determination

of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable  
5 pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets,  
10 dragees, capsules, or solutions.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating,  
15 emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally,  
20 suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes.  
25 Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the  
30 solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture,  
35 and processing the mixture of granules, after adding

suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

35

6. EXAMPLE: DP-178 (SEQ ID:1) IS A POTENT  
INHIBITOR OF HIV-1 INFECTION

In this example, DP-178 (SEQ ID:1) is shown to be a potent inhibitor of HIV-1 mediated CD-4<sup>+</sup> cell-cell fusion and infection by cell free virus. In the fusion assay, this peptide completely blocks virus induced syncytia formation at concentrations of from 1-10 ng/ml. In the infectivity assay the inhibitory concentration is somewhat higher, blocking infection at 90ng/ml. It is further shown that DP-178 (SEQ ID:1) shows that the antiviral activity of DP-178 (SEQ ID:1) is highly specific for HIV-1. Additionally, a synthetic peptide, DP-185 (SEQ ID:3), representing a HIV-1-derived DP-178 homolog is also found to block HIV-1-mediated syncytia formation.

15

6.1. MATERIALS AND METHODS

6.1.1. PEPTIDE SYNTHESIS

Peptides were synthesized using Fast Moc chemistry on an Applied Biosystems Model 431A peptide synthesizer. Amidated peptides were prepared using Rink resin (Advanced Chemtech) while peptides containing free carboxy termini were synthesized on Wang (p-alkoxy-benzyl-alcohol) resin (Bachem). First residues were double coupled to the appropriate resin and subsequent residues were single coupled. Each coupling step was followed by acetic anhydride capping. Peptides were cleaved from the resin by treatment with trifluoroacetic acid (TFA) (10ml), H<sub>2</sub>O (0.5ml), thioanisole (0.5ml), ethanedithiol (0.25ml), and crystalline phenol (0.75g). Purification was carried out by reverse phase HPLC. Approximately 50mg samples of crude peptide were chromatographed on a Waters Delta Pak C18 column (19mm x 30cm, 15μ spherical) with a linear gradient; H<sub>2</sub>O/acetonitrile

0.1% TFA. Lyophilized peptides were stored desiccated and peptide solutions were made in water at about 1mg/ml. Electrospray mass spectrometry yielded the following results: DP-178 (SEQ ID:1):4491.87 (calculated 4491.94); DP-180 (SEQ ID:2):4491.45 (calculated 4491.94); DP-185 (SEQ ID:3):not done (calculated 4546.97).

#### 6.1.2. VIRUS

The HIV-1<sub>LAI</sub> virus was obtained from R. Gallo (Popovic, M. et al., 1984, Science 224:497-508) and propagated in CEM cells cultured in RPMI 1640 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2 $\mu$ m filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this purpose, 25 $\mu$ l of serial diluted virus was added to 75 $\mu$ l AA5 cells at a concentration of  $2 \times 10^5$ /ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells were cultured for eight days by addition of fresh medium every other day. On day 8 post infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant. The TCID<sub>50</sub> was calculated according to the Reed and Muench formula (Reed, L.J. et al., 1938, Am. J. Hyg. 27:493-497). The titer of the HIV-1<sub>LAI</sub> and HIV-1<sub>MN</sub> stocks used for these studies, as measured on the AA5 cell line, was approximately  $1.4 \times 10^6$  and  $3.8 \times 10^4$  TCID<sub>50</sub>/ml, respectively.

#### 6.1.3. CELL FUSION ASSAY

Approximately  $7 \times 10^4$  Molt cells were incubated with  $1 \times 10^4$  CEM cells chronically infected with the HIV-1<sub>LAI</sub> virus in 96-well plates (one-half area cluster plates; Costar, Cambridge, MA) in a final volume of

100 $\mu$ l culture medium as previously described (Matthews, T.J. et al., 1987, Proc. Natl. Acad. Sci. USA 84: 5424-5428). Peptide inhibitors were added in a volume of 10 $\mu$ l and the cell mixtures were incubated for 24 hr. at 37°C. At that time, multinucleated  
5 giant cells were estimated by microscopic examination at a 40x magnification which allowed visualization of the entire well in a single field.

#### 6.1.4. CELL FREE VIRUS INFECTION ASSAY

10 Synthetic peptides were incubated at 37°C with either 247 TCID<sub>50</sub> (for experiment depicted in FIG. 2), or 62 TCID<sub>50</sub> (for experiment depicted in FIG.3) units of HIV-1<sub>LAI</sub> virus or 25 TCID<sub>50</sub> units of HIV-2<sub>NH2</sub> and CEM CD4<sup>+</sup> cells at peptide concentrations of 0, 0.04, 0.4,  
15 4.0, and 40 $\mu$ g/ml for 7 days. The resulting reverse transcriptase (RT) activity in counts per minute was determined using the assay described, below, in Section 6.1.5. See, Reed, L.J. et al., 1938, Am. J. Hyg. 27: 493-497 for an explanation of TCID<sub>50</sub>  
20 calculations.

#### 6.1.5. REVERSE TRANSCRIPTASE ASSAY

The micro-reverse transcriptase (RT) assay was adapted from Goff et al. (Goff, S. et al., 1981, J. Virol. 38:239-248) and Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). Supernatants from virus/cell cultures are adjusted to 1% Triton-X100. A  
25 10 $\mu$ l sample of supernatant was added to 50 $\mu$ l of RT cocktail in a 96-well U-bottom microtitre plate and the samples incubated at 37°C for 90 min. The RT  
30 cocktail contained 75mM KCl, 2mM dithiothreitol, 5mM MgCl<sub>2</sub>, 5 $\mu$ g/ml poly A (Pharmacia, cat. No. 27-4110-01), 0.25 units/ml oligo dT (Pharmacia, cat. No. 27-7858-01), 0.05% NP40, 50mM Tris-HCl, pH 7.8, 0.5 $\mu$ M non-  
35



radioactive dTTP, and 10 $\mu$ Ci/ml <sup>32</sup>P-dTTP (Amersham, cat. No. PB.10167).

After the incubation period, 40 $\mu$ l of reaction mixture was applied to a Schleicher and Schuell (S+S) NA45 membrane (or DE81 paper) saturated in 2 x SSC buffer (0.3M NaCl and 0.003M sodium citrate) held in a S+S Minifold over one sheet of GB003 (S+S) filter paper, with partial vacuum applied. Each well of the minifold was washed four times with 200 $\mu$ l 2xSSC, under full vacuum. The membrane was removed from the minifold and washed 2 more times in a pyrex dish with an excess of 2xSSC. Finally, the membrane was drained on absorbent paper, placed on Whatman #3 paper, covered with Saran wrap, and exposed to film overnight at -70°C.

## 6.2. RESULTS

### 6.2.1. PEPTIDE INHIBITION OF INFECTED CELL-INDUCED SYNCYTIA FORMATION

The initial screen for antiviral activity assayed peptides' ability to block syncytium formation induced by overnight co-cultivation of uninfected Molt4 cells with chronically HIV-1 infected CEM cells. The results of several such experiments are presented herein. In the first of these experiments, serial DP-178 (SEQ ID:1) peptide concentrations between 10 $\mu$ g/ml and 12.5ng/ml were tested for blockade of the cell fusion process. For these experiments, CEM cells chronically infected with either HIV-1<sub>LAI</sub>, HIV-1<sub>MN</sub>, HIV-1<sub>RF</sub>, or HIV-1<sub>SF2</sub> virus were cocultivated overnight with uninfected Molt 4 cells. The results (FIG. 4) show that DP-178 (SEQ ID:1) afforded complete protection against each of the HIV-1 isolates down to the lowest concentration of DP-178 (SEQ ID:1) used. For HIV<sub>LAI</sub> inhibition, the lowest concentration tested was

12.5ng/ml; for all other HIV-1 viruses, the lowest concentration of DP-178 (SEQ ID:1) used in this study was 100ng/ml. A second peptide, DP-180 (SEQ ID:2), containing the same amino acid residues as DP-178 (SEQ ID:1) but arranged in a random order exhibited no  
5 evidence of anti-fusogenic activity even at the high concentration of 40µg/ml (FIG. 4). These observations indicate that the inhibitory effect of DP-178 (SEQ ID:1) is primary sequence-specific and not related to non-specific peptide/protein interactions. The actual  
10 endpoint (*i.e.*, the lowest effective inhibitory concentration) of DP-178 inhibitory action is within the range of 1-10 ng/ml.

The next series of experiments involved the preparation and testing of a DP-178 (SEQ ID:1) homolog  
15 for its ability to inhibit HIV-1-induced syncytia formation. As shown in FIG. 1, the sequence of DP-185 (SEQ ID:3) is slightly different from DP-178 (SEQ ID:1) in that its primary sequence is taken from the HIV-1<sub>SF2</sub> isolate and contains several amino acid  
20 differences relative to DP-178 (SEQ ID:1) near the N terminus. As shown in FIG. 4, DP-185 (SEQ ID:3), exhibits inhibitory activity even at 312.5ng/ml, the lowest concentration tested.

The next series of experiments involved a  
25 comparison of DP-178 (SEQ ID:1) HIV-1 and HIV-2 inhibitory activity. As shown in FIG. 5, DP-178 (SEQ ID:1) blocked HIV-1-mediated syncytia formation at peptide concentrations below 1ng/ml. DP-178 (SEQ ID:1) failed, however, to block HIV-2 mediated  
30 syncytia formation at concentrations as high as 10µg/ml. This striking 4 log selectivity of DP-178 (SEQ ID:1) as an inhibitor of HIV-1-mediated cell fusion demonstrates an unexpected HIV-1 specificity in the action of DP-178 (SEQ ID:1). DP-178 (SEQ ID:1)  
35 inhibition of HIV-1-mediated cell fusion, but the

peptide's inability to inhibit HIV-2 medicated cell fusion in the same cell type at the concentrations tested provides further evidence for the high degree of selectivity associated with the antiviral action of DP-178 (SEQ ID:1).

5

6.2.2. PEPTIDE INHIBITION OF INFECTION BY  
CELL-FREE VIRUS

DP-178 (SEQ ID:1) was next tested for its ability to block CD-4<sup>+</sup> CEM cell infection by cell free HIV-1 virus. The results, shown in FIG. 2, are from an experiment in which DP-178 (SEQ ID:1) was assayed for its ability to block infection of CEM cells by an HIV-1<sub>LAI</sub> isolate. Included in the experiment were three control peptides, DP-116 (SEQ ID:9), DP-125 (SEQ ID:8), and DP-118 (SEQ ID:10). DP-116 (SEQ ID:9) represents a peptide previously shown to be inactive using this assay, and DP-125 (SEQ ID:8; Wild, C. et al., 1992, Proc. Natl. Acad. Sci. USA 89:10,537) and DP-118 (SEQ ID:10) are peptides which have previously been shown to be active in this assay. Each concentration (0, 0.04, 0.4, 4, and 40 $\mu$ g/ml) of peptide was incubated with 247 TCID<sub>50</sub> units of HIV-1<sub>LAI</sub> virus and CEM cells. After 7 days of culture, cell-free supernatant was tested for the presence of RT activity as a measure of successful infection. The results, shown in FIG. 2, demonstrate that DP-178 (SEQ ID:1) inhibited the de novo infection process mediated by the HIV-1 viral isolate at concentrations as low as 90ng/ml (IC<sub>50</sub>=90ng/ml). In contrast, the two positive control peptides, DP-125 (SEQ ID:8) and DP-118 (SEQ ID:10), had over 60-fold higher IC<sub>50</sub> concentrations of approximately 5 $\mu$ g/ml.

In a separate experiment, the HIV-1 and HIV-2 inhibitory action of DP-178 (SEQ ID:1) was tested with CEM cells and either HIV-1<sub>LAI</sub> or HIV-2<sub>NIHZ</sub>. 62 TCID<sub>50</sub>

HIV-1<sub>LAI</sub> or 25 GCID<sub>50</sub> HIV-2<sub>NIHZ</sub> were used in these experiments, and were incubated for 7 days. As may be seen in FIG. 3, DP-178 (SEQ ID:1) inhibited HIV-1 infection with an IC<sub>50</sub> of about 31ng/ml. In contrast, DP-178 (SEQ ID:1) exhibited a much higher IC<sub>50</sub> for HIV-2<sub>NIHZ</sub>, thus making DP-178 (SEQ ID:1) two logs more potent as a HIV-1 inhibitor than a HIV-2 inhibitor. This finding is consistent with the results of the fusion inhibition assays described, above, in Section 6.2.1, and further supports a significant level of selectivity (i.e., for HIV-1 over HIV-2).

7. EXAMPLE: THE HIV-1 INHIBITOR, DP-178 (SEQ ID:1) IS NON-CYTOXIC

In this Example, the 36 amino acid synthetic peptide inhibitor DP-178 (SEQ ID:1) is shown to be non-cytotoxic to cells in culture, even at the highest peptide concentrations (40µg/ml) tested.

7.1. MATERIALS AND METHODS

Cell proliferation and toxicity assay:  
Approximately 3.8x10<sup>5</sup> CEM cells for each peptide concentration were incubated for 3 days at 37°C in T25 flasks. Peptides tested were DP-178 (SEQ ID:1) and DP-116 (SEQ ID:9), as described in FIG. 1. The concentrations of each peptide used were 0, 2.5, 10, and 40µg/ml. Cell counts were taken at incubation times of 0, 24, 48, and 72 hours.

7.2. RESULTS

Whether the potent HIV-1 inhibitor DP-178 (SEQ ID:1) exhibited any cytotoxic effects was assessed by assaying the peptide's effects on the proliferation and viability of cells in culture. CEM cells were incubated in the presence of varying concentrations of DP-178 (SEQ ID:1), and DP-116 (SEQ ID:9), a peptide

previously shown to be ineffective as a HIV inhibitor (Wild, C. et al., 1992, Proc. Natl. Acad. Sci. USA 89:10,537-10,541). Additionally, cells were incubated in the absence of either peptide.

5 The results of the cytotoxicity study demonstrate that DP-178 (SEQ ID:1) exhibits no cytotoxic effects on cells in culture. As can be seen, below, in Table XI, even the proliferation and viability characteristics of cells cultured for 3 days in the presence of the highest concentration of DP-178 (SEQ  
10 ID:1) tested (40 $\mu$ g/ml) do not significantly differ from the DP-116 (SEQ ID:9) or the no-peptide controls. The cell proliferation data is also represented in graphic form in FIG. 6. As was demonstrated in the Working Example presented above in Section 6, DP-178  
15 (SEQ ID:1) completely inhibits HIV-1 mediated syncytia formation at peptide concentrations between 1 and 10ng/ml, and completely inhibits cell-free viral infection at concentrations of at least 90ng/ml. Thus, this study demonstrates that even at peptide  
20 concentrations greater than 3 log higher than the HIV inhibitory dose, DP-178 (SEQ ID:1) exhibits no cytotoxic effects.

TABLE XI

Peptide	Peptide Concentration $\mu$ g/ml	% Viability at time (hours)			
		0	24	48	72
30 DP178 (SEQ ID:1)	40	98	97	95	97
	10	98	97	98	98
	2.5	98	93	96	96
35					

5	DP116 (SEQ ID:9)	40	98	95	98	97
		10	98	95	93	98
		2.5	98	96	98	99
	No Peptide	0	98	97	99	98

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## 10 8. EXAMPLE: THE INTERACTION OF DP178 AND DP107

15 Soluble recombinant forms of gp41 used in the example described below provide evidence that the DP178 peptide associates with a distal site on gp41 whose interactive structure is influenced by the DP107 leucine zipper motif. A single mutation disrupting the coiled-coil structure of the leucine zipper domain transformed the soluble recombinant gp41 protein from an inactive to an active inhibitor of HIV-1 fusion. This transformation may result from liberation of the potent DP178 domain from a molecular clasp with the leucine zipper, DP107, determinant. The results also indicate that the anti-HIV activity of various gp41 derivatives (peptides and recombinant proteins) may be due to their ability to form complexes with viral gp41 and interfere with its fusogenic process.

### 8.1. MATERIALS AND METHODS

#### 8.1.1. CONSTRUCTION OF FUSION PROTEINS AND GP41 MUTANTS

30 Construction of fusion proteins and mutants shown in FIG. 7 was accomplished as follows: the DNA sequence corresponding to the extracellular domain of gp41 (540-686) was cloned into the Xmn I site of the expression vector pMal-p2 (New England Biolab) to give 35 M41. The gp41 sequence was amplified from pgtat

(Malim et al., 1988, Nature 355: 181-183) by using polymerase chain reaction (PCR) with upstream primer 5'-ATGACGCTGACGGTACAGGCC-3' (primer A) and downstream primer 5'-TGACTAAGCTTAATACCACAGCCAATTTGTTAT-3' (primer B). M41-P was constructed by using the T7-Gen  
5 in vitro mutagenesis kit from United States Biochemicals (USB) following the supplier's instructions. The mutagenic primer (5'-GGAGCTGCTTGGGGCCCCAGAC-3') introduces an Ile to Pro mutation in M41 at position 578. M41 $\Delta$ 107 was made  
10 using a deletion mutagenic primer 5'-CCAAATCCCCAGGAGCTGCTCGAGCTGCACTATACCAGAC-3' (primer C) following the USB T7-Gen mutagenesis protocol. M41 $\Delta$ 178 was made by cloning the DNA fragment corresponding to gp41 amino acids 540-642 into the Xmn  
15 I site of pMal-p2. Primer A and 5'-ATAGCTTCTAGATTAATTGTTAATTTCTCTGTCCC-3' (primer D) were used in the PCR with the template pgtat to generate the inserted DNA fragments. M41-P was used as the template with primer A and D in PCR to generate M41-  
20 PA178. All inserted sequences and mutated residues were checked by restriction enzyme analysis and confirmed by DNA sequencing.

#### 25 8.1.2. PURIFICATION AND CHARACTERIZATION OF FUSION PROTEINS

The fusion proteins were purified according to the protocol described in the manufacturer's brochure of protein fusion and purification systems from New England Biolabs (NEB). Fusion proteins (10 ng) were  
30 analyzed by electrophoresis on 8% SDS polyacrylamide gels. Western blotting analysis was performed as described by Sambrook et al, 1989, Molecular Cloning: A Laboratory Manual, 2d Ed, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, Ch. 18,  
35 pp. 64-75. An HIV-1 positive serum diluted 1000-fold,

or a human Fab derived from repertoire cloning was used to react with the fusion proteins. The second antibody was HRP-conjugated goat antihuman Fab. An ECL Western blotting detection system (Amersham) was used to detect the bound antibody. A detailed  
5 protocol for this detection system was provided by the manufacturer. Rainbow molecular weight marker (Amersham) were used to estimate the size of fusion proteins.

10 8.1.3. CELL FUSION ASSAYS FOR ANTI-HIV ACTIVITY

Cell fusion assays were performed as previously described (Matthews et al., 1987, Proc. Natl. Acad. Sci. USA 84: 5424-5481). CEM cells ( $7 \times 10^4$ ) were  
15 incubated with HIV-1<sub>MB</sub> chronically infected CEM cells ( $10^4$ ) in 96-well flat-bottomed half-area plates (Costar) in 100  $\mu$ l culture medium. Peptide and fusion proteins at various concentrations in 10  $\mu$ l culture medium were incubated with the cell mixtures at 37°C for 24 hours. Multinucleated syncytia were estimated  
20 with microscopic examination. Both M41 and M41-P did not show cytotoxicity at the concentrations tested and shown in FIG. 8.

Inhibition of HIV-1 induced cell-cell fusion activity was carried out in the presence of 10 nM  
25 DP178 and various concentrations of M41 $\Delta$ 178 or M41-PA178 as indicated in FIG. 9. There was no observable syncytia in the presence of 10 nM DP178. No peptide or fusion protein was added in the control samples.

30 8.1.4. ELISA ANALYSIS OF DP178 BINDING TO THE LEUCINE ZIPPER MOTIF OF GP41

The amino acid sequence of DP178 used is:  
YTSLIHSLIEESQNQQEKNEQELLELDKQASLWNWF. For enzyme  
linked immunoassay (ELISA), M41 $\Delta$ 178 or M41-PA178 (5  
35  $\mu$ g/ml) in 0.1M NaHCO<sub>3</sub>, pH 8.6, were coated on 96 wells



Linbro ELISA plates (Flow Lab, Inc.) overnight. Each well was washed three times with distilled water then blocked with 3% bovine serum albumin (BSA) for 2 hours. After blocking, peptides with 0.5% BSA in TBST (40 mM Tris-HCl pH7.5, 150 mM NaCl, 0.05% Tween 20) were added to the ELISA plates and incubated at room temperature for 1 hour. After washing three times with TBST, Fab-d was added at a concentration of 10 ng/ml with 0.5% BSA in TBST. The plates were washed three times with TBST after incubation at room temperature for 1 hour. Horse radish peroxidase (HRP) conjugated goat antihuman Fab antiserum at a 2000 fold dilution in TBST with 0.5% BSA was added to each well and incubated at room temperature for 45 minutes. The plates were then washed four times with TBST. The peroxidase substrate o-phenylene diamine (2.5 mg/ml) and 0.15% H<sub>2</sub>O<sub>2</sub> were added to develop the color. The reaction was stopped with an equal volume of 4.5 N H<sub>2</sub>SO<sub>4</sub> after incubation at room temperature for 10 minutes. The optical density of the stopped reaction mixture was measured with a micro plate reader (Molecular Design) at 490 nm. Results are shown in FIG. 10.

## 8.2. RESULTS

### 8.2.1. THE EXPRESSION AND CHARACTERIZATION OF THE ECTODOMAIN OF GP41

As a step toward understanding the roles of the two helical regions in gp41 structure and function, the ectodomain of gp41 was expressed as a maltose binding fusion protein (M41) (Fig. 7). The fusogenic peptide sequence at the N-terminal of gp41 was omitted from this recombinant protein and its derivatives to improve solubility. The maltose binding protein facilitated purification of the fusion proteins under relatively mild, non-denaturing conditions. Because

the M41 soluble recombinant gp41 was not glycosylated, lacked several regions of the transmembrane protein (i.e., the fusion peptide, the membrane spanning, and the cytoplasmic domains), and was expressed in the absence of gp120, it was not expected to precisely reflect the structure of native gp41 on HIV-1 virions. Nevertheless, purified M41 folded in a manner that preserved certain discontinuous epitopes as evidenced by reactivity with human monoclonal antibodies, 98-6, 126-6, and 50-69, previously shown to bind conformational epitopes on native gp41 expressed in eukaryotic cells (Xu et al., 1991, J. Virol. 65: 4832-4838; Chen, 1994, J. Virol. 68:2002-2010). Thus, at least certain regions of native gp41 defined by these antibodies appear to be reproduced in the recombinant fusion protein M41. Furthermore, M41 reacted with a human recombinant Fab (Fab-d) that recognizes a conformational epitope on gp41 and binds HIV-1 virions as well as HIV-1 infected cells but not uninfected cells as analyzed by FACS. Deletion of either helix motif, i.e., DP107 or DP178, of the M41 fusion protein eliminated reactivity with Fab-d. These results indicate that both helical regions, separated by 60 amino acids in the primary sequence, are required to maintain the Fab-d epitope.

#### 8.2.2. ANTI-HIV ACTIVITY OF THE RECOMBINANT ECTODOMAIN OF GP41

The wild type M41 fusion protein was tested for anti-HIV-1 activity. As explained, supra, synthetic peptides corresponding to the leucine zipper (DP107) and the C-terminal putative helix (DP178) show potent anti-HIV activity. Despite inclusion of both these regions, the recombinant M41 protein did not affect

HIV-1 induced membrane fusion at concentrations as high as 50  $\mu$ M (Table XII, below).

**TABLE XII**  
**DISRUPTION OF THE LEUCINE ZIPPER OF**  
**GP41 FREES THE ANTI-HIV MOTIF**

	<u>DP107</u>	<u>DP178</u>	<u>M41</u>	<u>M41-P</u>	<u>M41-PA178</u>
Cell fusion (IC <sub>90</sub> )	1 $\mu$ M	1 nM	> 50 $\mu$ M	83 nM	> 50 $\mu$ M
Fab-D binding (k <sub>D</sub> )	-	-	3.5x10 <sup>-9</sup>	2.5x10 <sup>-8</sup>	-
HIV infectiv- ity (IC <sub>90</sub> )	1 $\mu$ M	80 nM	> 16 $\mu$ M	66 nM	> 8 $\mu$ M

The affinity constants of Fab-d binding to the fusion proteins were determined using a protocol described by B. Friguet et al., 1985, J. Immunol. Method. 77:305-319.

- = No detectable binding of Fab-d to the fusion proteins.

*Antiviral Infectivity Assays.* 20  $\mu$ l of serially diluted virus stock was incubated for 60 minutes at ambient temperature with 20  $\mu$ l of the indicated concentration of purified recombinant fusion protein in RPMI 1640 containing 10% fetal bovine serum and antibiotics in a 96-well microtiter plate. 20  $\mu$ l of CEM4 cells at 6 x 10<sup>5</sup> cells/ml were added to each well, and cultures were incubated at 37°C in a humidified CO<sub>2</sub> incubator. Cells were cultured for 9 days by the addition of fresh medium every 2 to 30 days. On days 5, 7, and 9 postinfection, supernatant samples were assayed for reverse transcriptase (RT) activity, as described below, to monitor viral replication. The 50% tissue culture infectious dose (TCID<sub>50</sub>) was calculated for each condition according to the formula of Reed & Muench, 1937, Am. J. Hyg. 27:493-497. RT activity was determined by a modification of the published methods of Goff et al., 1981, J. Virol. 38:239-248 and Willey et al., 1988, J. Virol. 62:139-147 as described in Chen et al., 1993, AIDS Res. Human Retroviruses 9:1079-1086.

Surprisingly, a single amino acid substitution, proline in place of isoleucine in the middle of the leucine zipper motif, yielded a fusion protein (M41-P)

which did exhibit antiviral activity (Table XII and Fig. 8). As seen in Table XII, M41-P blocked syncytia formation by 90% at approximately 85 nM and neutralized HIV-1<sub>III</sub> infection by 90% at approximately 70 nM concentrations. The anti-HIV-1 activity of M41-P appeared to be mediated by the C-terminal helical sequence since deletion of that region from M41-P yielded an inactive fusion protein, M41-PA178 (Table XII). That interpretation was reinforced by experiments demonstrating that a truncated fusion protein lacking the DP178 sequence, M41Δ178, abrogated the potent anti-fusion activity of the DP178 peptide in a concentration-dependent manner (FIG. 9). The same truncated fusion protein containing the proline mutation disrupting the leucine zipper, M41-PA178, was not active in similar competition experiments (FIG. 9). The results indicate that the DP178 peptide associates with a second site on gp41 whose interactive structure is dependent on a wild type leucine zipper sequence. A similar interaction may occur within the wild type fusion protein, M41, and act to form an intramolecular clasp which sequesters the DP178 region, making it unavailable for anti-viral activity.

A specific association between these two domains is also indicated by other human monoclonal Fab-d studies. For example, Fab-d failed to bind either the DP178 peptide or the fusion protein M41Δ178, but its epitope was reconstituted by simply mixing these two reagents together (FIG. 10). Again, the proline mutation in the leucine zipper domain of the fusion protein, M41-PA178, failed to reconstitute the epitope in similar mixing experiments.

9. EXAMPLE: METHOD FOR COMPUTER-ASSISTED  
IDENTIFICATION OF DP-107-LIKE  
AND DP-178-LIKE SEQUENCES

A number of known coiled-coil sequences have been well described in the literature and contain heptad repeat positioning for each amino acid. Coiled-coil nomenclature labels each of seven amino acids of a heptad repeat A through G, with amino acids A and D tending to be hydrophobic positions. Amino acids E and G tend to be charged. These four positions (A, D, E, and G) form the amphipathic backbone structure of a monomeric alpha-helix. The backbones of two or more amphipathic helices interact with each other to form di-, tri-, tetrameric, etc., coiled-coil structures. In order to begin to design computer search motifs, a series of well characterized coiled coils were chosen including yeast transcription factor GCN4, Influenza Virus hemagglutinin loop 36, and human proto-oncogenes c-Myc, c-Fos, and c-Jun. For each peptide sequence, a strict homology for the A and D positions, and a list of the amino acids which could be excluded for the B, C, E, F, and G positions (because they are not observed in these positions) was determined. Motifs were tailored to the DP-107 and DP-178 sequences by deducing the most likely possibilities for heptad positioning of the amino acids of HIV-1 Bru DP-107, which is known to have coiled-coil structure, and HIV-1 Bru DP-178, which is still structurally undefined. The analysis of each of the sequences is contained in FIG. 12. For example, the motif for GCN4 was designed as follows:

1. The only amino acids (using standard single letter amino acid codes) found in the A or D positions of GCN4 were [LMNV].
2. All amino acids were found at B, C, E, F, and G positions except {CFGIMPTW}.

3. The PESEARCH motif would, therefore, be written as follows:

[LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-  
 [LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-  
 [LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-  
 5 [LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)

Translating or reading the motif: "at the first A position either L, M, N, or V must occur; at positions B and C (the next two positions) accept everything  
 10 except C, F, G, I, M, P, T, or W; at the D position either L, M, N, or V must occur; at positions E, F, and G (the next 3 positions) accept everything except C, F, G, I, M, P, T, or W." This statement is  
 15 contained four times in a 28-mer motif and five times in a 35-mer motif. The basic motif key then would be: [LMNV]-{CFGIMPTW}. The motif keys for the remaining well described coiled-coil sequences are summarized in FIG. 12.

The motif design for DP-107 and DP-178 was  
 20 slightly different than the 28-mer model sequences described above due to the fact that heptad repeat positions are not defined and the peptides are both longer than 28 residues. FIG. 13 illustrates several possible sequence alignments for both DP-107 and DP-  
 25 178 and also includes motif designs based on 28<sup>-mer</sup>, 35<sup>-mer</sup>, and full-length peptides. Notice that only slight differences occur in the motifs as the peptides are lengthened. Generally, lengthening the base peptide results in a less stringent motif. This is  
 30 very useful in broadening the possibilities for identifying DP-107-or DP-178-like primary amino acid sequences referred to in this document as "hits".

In addition to making highly specific motifs for  
 35 each type peptide sequence to be searched, it is also possible to make "hybrid" motifs. These motifs are

made by "crossing" two or more very stringent motifs to make a new search algorithm which will find not only both "parent" motif sequences but also any peptide sequences which have similarities to one, the other, or both "parents". For example, in Table 3 the "parent" sequence of GCN4 is crossed with each of the possible "parent" motifs of DP-107. Now the hybrid motif must contain all of the amino acids found in the A and D positions of both parents, and exclude all of the amino acids not found in either parent at the other positions. The resulting hybrid from crossing GCN4 or [LMNV]{CFGIMPTW} and DP-107 (28-mer with the first L in the D position) or [ILQT]{CDFIMPST}, is [ILMNQTV]{CFIMPT}. Notice that now only two basic hybrid motifs exist which cover both framing possibilities, as well as all peptide lengths of the parent DP-107 molecule. FIG. 15 represents the hybridizations of GCN4 with DP-178. FIG. 16 represents the hybridizations of DP-107 and DP-178. It is important to keep in mind that the represented motifs, both parent and hybrid, are motif keys and not the depiction of the full-length motif needed to actually do the computer search.

Hybridizations can be performed on any combination of two or more motifs. Table 5 summarizes several three-motif hybridizations including GCN4, DP-107 (both frames), and DP-178 (also both frames). Notice that the resulting motifs are now becoming much more similar to each other. In fact, the first and third hybrid motifs are actually subsets of the second and fourth hybrid motifs respectively. This means that the first and third hybrid motifs are slightly more stringent than the second and fourth. It should also be noted that with only minor changes in these four motifs, or by hybridizing them, a single motif could be obtained

which would find all of the sequences. However, it should be remembered that stringency is also reduced. Finally, the most broad-spectra and least-stringent hybrid motif is described in FIG. 18 which summarizes the hybridization of GCN4, DP-107 (both frames), DP-178 (both frames), c-Fos, c-Jun, c-Myc, and Flu loop 36.

A special set of motifs was designed based on the fact that DP-178 is located only approximately ten amino acids upstream of the transmembrane spanning region of gp41 and just C-terminal to a proline which separates DP-107 and DP-178. It has postulated that DP-178 may be an amphipathic helix when membrane associated, and that the proline might aid in the initiation of the helix formation. The same arrangement was observed in Respiratory Syncytial Virus; however, the DP-178-like region in this virus also had a leucine zipper just C-terminal to the proline. Therefore, designed N-terminal proline-leucine zipper motifs were designed to analyze whether any other viruses might contain this same pattern. The motifs are summarized in FIG. 19.

The PC/Gene protein database contains 5879 viral amino acid sequences (library file PVIRUSES; CD-ROM release 11.0). Of these, 1092 are viral envelope or glycoprotein sequences (library file PVIRUSE1). Tables V through X contain lists of protein sequence names and motif hit locations for all the motifs searched.

10. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION  
OF DP-107 AND DP-178-LIKE SEQUENCES  
IN HUMAN IMMUNODEFICIENCY VIRUS

FIG. 20 represents search results for HIV-1 BRU isolate gp41 (PC/Gene protein sequence PENV\_HV1BR). Notice that the hybrid motif which crosses DP-107 and



DP-178 (named 107x178x4; the same motif as found in FIG. 16 found three hits including amino acids 550-599, 636-688, and 796-823. These areas include DP-107 plus eight N-terminal and four C-terminal amino acids; DP-178 plus seven N-terminal and ten C-terminal amino acids; and an area inside the transmembrane region (cytoplasmic). FIG. 20 also contains the results obtained from searching with the motif named ALLMOTI5, for which the key is found in FIG. 17 ({CDGHP}{CFP}x5). This motif also found three hits including DP-107 (amino acids 510-599), DP-178 (615-717), and a cytoplasmic region (772-841). These hits overlap the hits found by the motif 107x178x4 with considerable additional sequences on both the amino and carboxy termini. This is not surprising in that 107x178x4 is a subset of the ALLMOTI5 hybrid motif. Importantly, even though the stringency of ALLMOTI5 is considerably less than 107x178x4, it still selectively identifies the DP-107 and DP-178 regions of gp41 shown to contain sequences for inhibitory peptides of HIV-1. The results of these two motif searches are summarized in Table V under the PC/Gene protein sequence name PENV HV1BR. The proline-leucine zipper motifs also gave several hits in HIV-1 BRU including 503-525 which is at the very C-terminus of gp120, just upstream of the cleavage site (P7LZIPC and P12LZIPC); and 735-768 in the cytoplasmic domain of gp41 (P23LZIPC). These results are found in Tables VIII, IX, and X under the same sequence name as mentioned above. Notice that the only area of HIV-1 BRU which is predicted by the Lupas algorithm to contain a coiled-coil region, is from amino acids 635-670. This begins eight amino acids N-terminal to the start and ends eight amino acids N-terminal to the end of DP-178. DP-107, despite the fact that it is a known coiled coil, is

not predicted to contain a coiled-coil region using the Lupas method.

11. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION  
OF DP-107-LIKE AND DP-178-LIKE  
SEQUENCES IN HUMAN RESPIRATORY  
SYNCYTIAL VIRUS

FIG. 21 represents search results for Human Respiratory Syncytial Virus (RSV; Strain A2) fusion glycoprotein F1 (PC/Gene protein sequence name PVGLF\_HRSVA). Motif 107x178x4 finds three hits including amino acids 152-202, 213-243, and 488-515. The arrangement of these hits is similar to what is found in HIV-1 except that the motif finds two regions with similarities to DP-178, one just downstream of what would be called the DP-107 region or amino acids 213-243, and one just upstream of the transmembrane region (also similar to DP-178) or amino acids 488-515. Motif ALLMOTI5 also finds three areas including amino acids 116-202, 267-302, and 506-549. The proline-leucine zipper motifs also gave several hits including amino acids 205-221 and 265-287 (P1LZIPC 265-280, P12LZIPC), and 484-513 (P7LZIPC and P12LZIPC 484-506, P23LZIPC). Notice that the PLZIP motifs also identify regions which share location similarities with DP-178 of HIV-1.

12. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF  
DP-107-LIKE AND DP-178-LIKE SEQUENCES  
IN SIMIAN IMMUNODEFICIENCY VIRUS

Motif hits for Simian immunodeficiency Virus gp41 (AGM3 isolate; PC/Gene protein sequence name PENV\_SIVAG) are shown in FIG. 22. Motif 107x178x4 finds three hits including amino acids 566-593, 597-624, and 703-730. The first two hits only have three amino acids between them and could probably be combined into one hit from 566-624 which would

represent a DP-107-like hit. Amino acids 703 to 730 would then represent a DP-178-like hit. ALLMOTI5 also finds three hits including amino acids 556-628 (DP-107-like), 651-699 (DP-178-like), and 808-852 which represents the transmembrane spanning region. SIV  
5 also has one region from 655-692 with a high propensity to form a coiled coil as predicted by the Lupas algorithm. Both 107x178x4 and ALLMOTI5 motifs find the same region. SIV does not have any PLZIP motif hits in gp41.  
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13. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF  
DP-107-LIKE AND DP-178 LIKE SEQUENCES  
IN CANINE DISTEMPER VIRUS

Canine Distemper Virus (strain Onderstepoort)  
15 fusion glycoprotein F1 (PC/Gene Protein sequence name PVGLF\_CDVO) has regions similar to Human RSV which are predicted to be DP-107-like and DP-178-like (FIG. 23). Motif 107x178x4 highlights one area just C-terminal to the fusion peptide at amino acids 252-293. Amino  
20 acids 252-286 are also predicted to be coiled coil using the Lupas algorithm. Almost 100 amino acids C-terminal to the first region is a DP-178-like area at residues 340-367. ALLMOTI5 highlights three areas of interest including: amino acids 228-297, which  
25 completely overlaps both the Lupas prediction and the DP-107-like 107x178x4 hit; residues 340-381, which overlaps the second 107x178x4 hit; and amino acids 568-602, which is DP178-like in that it is located just N-terminal to the transmembrane region. It also  
30 overlaps another region (residues 570-602) predicted by the Lupas method to have a high propensity to form a coiled coil. Several PLZIP motifs successfully identified areas of interest including P6 and P12LZIPC which highlight residues 336-357 and 336-361  
35 respectively; P1 and P12LZIPC which find residues 398-

414; and P12 and P23LZIPC which find residues 562-589 and 562-592 respectively.

14. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF  
DP-107-LIKE AND DP-178-LIKE SEQUENCES  
IN NEWCASTLE DISEASE VIRUS

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FIG. 24 shows the motif hits found in Newcastle Disease Virus (strain Australia-Victoria/32; PC Gene protein sequence name PVGLF\_NDVA). Motif 107x178x4 finds two areas including a DP-107-like hit at amino acids 151-178 and a DP-178-like hit at residues 426-512. ALLMOTI5 finds three areas including residues 117-182, 231-272, and 426-512. The hits from 426-512 include a region which is predicted by the Lupas method to have a high coiled-coil propensity (460-503). The PLZIP motifs identify only one region of interest at amino acids 273-289 (P1 and 12LZIPC).

15. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION  
OF DP-107-LIKE AND DP-178-LIKE  
SEQUENCES IN HUMAN PARAINFLUENZA VIRUS

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Both motifs 107x178x4 and ALLMOTI5 exhibit DP-107-like hits in the same region, 115-182 and 117-182 respectively, of Human Parainfluenza Virus (strain NIH 47885; PC/Gene protein sequence name PVGLF\_p13H4; (FIG. 25). In addition, the two motifs have a DP-178-like hit just slightly C-terminal at amino acids 207-241. Both motifs also have DP-178-like hits nearer the transmembrane region including amino acids 457-497 and 462-512 respectively. Several PLZIP motif hits are also observed including 283-303 (P5LZIPC), 283-310 (P12LZIPC), 453-474 (P6LZIPC), and 453-481 (P23LZIPC). The Lupas algorithm predicts that amino acids 122-176 have a propensity to form a coiled-coil.

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16. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF  
DP-107-LIKE AND DP-178-LIKE SEQUENCES OF  
INFLUENZA A VIRUS

FIG. 26 illustrates the Lupas prediction for a coiled coil in Influenza A Virus (strain A/Aichi/2/68) at residues 379-436, as well as the motif hits for 107x178x4 at amino acids 387-453, and for ALLMOTI5 at residues 380-456. Residues 383-471 (38-125 of HA2) were shown by Carr and Kim to be an extended coiled coil when under acidic pH (Carr and Kim, 1993, Cell 73: 823-832). The Lupas algorithm predicts a coiled-coil at residues 379-436. All three methods successfully predicted the region shown to actually have coiled-coil structure; however, ALLMOTI5 predicted the greatest portion of the 88 residue stretch.

17. EXAMPLE: RSV ANTIVIRAL COMPOUNDS

In the Example presented herein, respiratory syncytial virus (RSV) peptide sequences identified by utilizing the computer-assisted coiled-coil peptide sequence searches described in Example 9, above, are shown to encode peptide domains that exhibit structural similarity to actual, known coiled-coil peptides, and are, additionally found to exhibit antiviral activity.

17.1 MATERIALS AND METHODS

Structural analyses consisted of circular dichroism (CD) studies, which were conducted according to the methods described in the Applicants' co-pending U.S. Patent Application Ser. No 08/073,028.

Anti-RSV antiviral activity was assayed as described in Pringle, C.R. et al., 1985, J. Medical Vir. 17:377-386.

A 48 amino acid RSV F2 peptide and a 53 amino acid RSV T67 peptide are utilized which span sequences that were identified via the computer assisted peptide sequence search strategies described in Example 9, above. See FIG. 21 for the exact position of these sequences and for the motifs utilized.

## 17.2 RESULTS

35-mer oligopeptides were synthesized which constituted portions of the 48 amino acid RSV F2 peptide sequence (FIG. 27) and portions of the 53 amino acid RSV T67 peptide sequence (FIG. 28). The oligopeptides were assayed, via CD analysis, for structural similarity to known coiled-coil structures, and for anti-RSV activity. As shown in FIGS. 27 and 28, a number of these oligopeptides exhibited substantial coiled-coil structural similarity and/or antiviral activity.

Thus, the computer assisted searches described, herein, in Example 9, for example, successfully identified viral peptide domains that represent highly promising anti-RSV antiviral compounds.

## 18. EXAMPLE: HPF3 ANTIVIRAL COMPOUNDS

In the Example presented herein, human parainfluenza virus 3 (HPF3) peptide sequences identified by utilizing the computer-assisted coiled-coil peptide sequence searches described in Example 9, above, are shown to encode peptide domains that exhibit structural similarity to actual, known coiled-coil peptides, and are, additionally found to exhibit antiviral activity.

### 18.1 MATERIALS AND METHODS

Structural analyses consisted of circular dichroism (CD) studies, which were conducted according

to the methods described in the Applicants' co-pending U.S. Patent Application Ser. No 08/073,028.

Anti-HPF3 antiviral activity was assayed as described in Pringle, C.R. et al., 1985, J. Medical Vir. 17:377-386.

5       A 56 amino acid and 70 amino acid HPF3 peptide are utilized which span sequences that were identified via the computer assisted peptide sequence search strategies described in Example 9, above. See FIG. 25 for the exact positions of these sequences and for the  
10 motifs utilized.

## 18.2 RESULTS

35-mer oligopeptides were synthesized which constituted portions of the 56 amino acid HPF3 peptide  
15 sequence (FIG. 29) and portions of the 70 amino acid HPF3 peptide sequence (FIG. 30). The oligopeptides were assayed, via CD analysis, for structural similarity to known coiled-coil structures, and for  
20 anti-HPF3 activity. As shown in FIGS. 29 and 30, a number of these oligopeptides exhibited substantial coiled-coil structural similarity and/or antiviral activity.

Thus, the computer assisted searches described, herein, in Example 9, for example, successfully  
25 identified viral peptide domains that represent highly promising anti-HPF3 antiviral compounds.

The present invention is not to be limited in scope by the specific embodiments described which are  
30 intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will  
35 become apparent to those skilled in the art from the

foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A peptide having an amino acid sequence corresponding to an  $\alpha$ -helix region of an extracellular domain of a viral envelope protein, which interacts  
5 with and binds to a second  $\alpha$ -helix region of the viral envelope protein containing a leucine-zipper domain having a coiled-coil structure.
- 10 2. The peptide of Claim 1 wherein the peptide is recognized by a computer-assisted peptide sequence search utilizing an ALLMOTI5, 107x178x4 motif, or a PLZIP motif.
- 15 3. The peptide of Claim 1 in which the enveloped virus is a retrovirus.
- 20 4. The peptide of Claim 3 in which the retrovirus is a human retrovirus.
- 25 5. The peptide of Claim 4 in which the human retrovirus is HIV-1 or HIV-2.
6. The peptide of Claim 4 in which the human retrovirus is HTLV-I or HTLV-II
7. The peptide of Claim 1 in which the enveloped virus is a non-human retrovirus.
8. The peptide of Claim 6 in which the non-  
30 human retrovirus is bovine leukosis virus, feline sarcoma virus, feline leukemia virus, simian immunodeficiency virus, simian sarcoma virus, and sheep progress pneumonia virus.

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9. The peptide of Claim 1 in which the enveloped virus is a non-retroviral virus.

10. The peptide of Claim 9 in which the virus is respiratory syncytial virus, influenza virus,  
5 parainfluenza virus, canine distemper virus, or newcastle disease virus.

11. A peptide having a formula selected from the group consisting of:

10 X-YTS-Z  
X-YTSL-Z  
X-YTSLI-Z  
X-YTSLIH-Z  
X-YTSLIHS-Z  
X-YTSLIHSL-Z  
X-YTSLIHSLI-Z  
15 X-YTSLIHSLIE-Z  
X-YTSLIHSLIEE-Z  
X-YTSLIHSLIEES-Z  
X-YTSLIHSLIEESQ-Z  
X-YTSLIHSLIEESQN-Z  
X-YTSLIHSLIEESQNNQ-Z  
X-YTSLIHSLIEESQNNQQ-Z  
X-YTSLIHSLIEESQNNQQE-Z  
20 X-YTSLIHSLIEESQNNQQEK-Z  
X-YTSLIHSLIEESQNNQQEKN-Z  
X-YTSLIHSLIEESQNNQQEKNE-Z  
X-YTSLIHSLIEESQNNQQEKNEQ-Z  
X-YTSLIHSLIEESQNNQQEKNEQE-Z  
X-YTSLIHSLIEESQNNQQEKNEQEL-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLE-Z  
25 X-YTSLIHSLIEESQNNQQEKNEQELLEL-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELD-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDK-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKW-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKWA-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKWas-Z  
30 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWasL-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKWasLW-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKWasLWN-Z  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKWasLWNW-Z and  
X-YTSLIHSLIEESQNNQQEKNEQELLELDKWasLWNWF-Z (SEQ ID:1), or

35

X-NWF-Z  
 X-WNWF-Z  
 X-LWNWF-Z  
 X-SLWNWF-Z  
 X-ASLWNWF-Z  
 X-WASLWNWF-Z  
 X-KWASLWNWF-Z  
 5 X-DKWASLWNWF-Z  
 X-LDKWASLWNWF-Z  
 X-ELDKWASLWNWF-Z  
 X-LELDKWASLWNWF-Z  
 X-LLELDKWASLWNWF-Z  
 X-ELLELDKWASLWNWF-Z  
 X-QELLELDKWASLWNWF-Z  
 X-EQELLELDKWASLWNWF-Z  
 10 X-NEQELLELDKWASLWNWF-Z  
 X-KNEQELLELDKWASLWNWF-Z  
 X-EKNEQELLELDKWASLWNWF-Z  
 X-QEKNEQELLELDKWASLWNWF-Z  
 X-QQEKNEQELLELDKWASLWNWF-Z  
 X-NQQEKNEQELLELDKWASLWNWF-Z  
 X-QNQQEKNEQELLELDKWASLWNWF-Z  
 15 X-SQNQQEKNEQELLELDKWASLWNWF-Z  
 X-ESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-EESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-IEESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-LIEESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-SLIEESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-HSLIEESQNQQEKNEQELLELDKWASLWNWF-Z  
 20 X-IHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z  
 X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z  
 and X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z

in which:

25 amino acid residues are presented by the single-letter code;  
 X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecule carrier group;  
 30 Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

35 12. A peptide having a formula selected from the group consisting of:

X-LEA-Z  
 X-LEAN-Z  
 X-LEANI-Z  
 X-LEANIS-Z  
 X-LEANISQ-Z  
 X-LEANISQS-Z  
 X-LEANISQSL-Z  
 5 X-LEANISQSLE-Z  
 X-LEANISQSLEQ-Z  
 X-LEANISQSLEQA-Z  
 X-LEANISQSLEQAQ-Z  
 X-LEANISQSLEQAQI-Z  
 X-LEANISQSLEQAQIQ-Z  
 X-LEANISQSLEQAQIQQ-Z  
 10 X-LEANISQSLEQAQIQQE-Z  
 X-LEANISQSLEQAQIQQEK-Z  
 X-LEANISQSLEQAQIQQEKN-Z  
 X-LEANISQSLEQAQIQQEKNM-Z  
 X-LEANISQSLEQAQIQQEKNMY-Z  
 X-LEANISQSLEQAQIQQEKNMYE-Z  
 X-LEANISQSLEQAQIQQEKNMYEL-Z  
 X-LEANISQSLEQAQIQQEKNMYELQ-Z  
 15 X-LEANISQSLEQAQIQQEKNMYELQK-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKL-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLN-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLNS-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLNSW-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWD-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDV-Z  
 20 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN-Z  
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW-Z and  
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z (SEQ ID:7), or

X-NWL-Z  
 X-TNWL-Z  
 25 X-FTNWL-Z  
 X-VFTNWL-Z  
 X-DVFTNWL-Z  
 X-WDVFTNWL-Z  
 X-SWDVFTNWL-Z  
 X-NSWDVFTNWL-Z  
 X-LNSWDVFTNWL-Z  
 30 X-KLNSWDVFTNWL-Z  
 X-QKLNSWDVFTNWL-Z  
 X-LQKLNSWDVFTNWL-Z  
 X-ELQKLNSWDVFTNWL-Z  
 X-YELQKLNSWDVFTNWL-Z  
 X-MYELQKLNSWDVFTNWL-Z  
 X-NMYELQKLNSWDVFTNWL-Z  
 X-KNMYELQKLNSWDVFTNWL-Z  
 35 X-EKNMYELQKLNSWDVFTNWL-Z  
 X-QEKNMYELQKLNSWDVFTNWL-Z

X-QQEKKNMYELQKLNSWDVFTNWL-Z  
 X-IQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-QIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-AQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-QAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-EQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-LEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-SLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-QKSLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-SQSLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-ISQSLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-NISQSLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 X-ANISQSLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z  
 and X-EANISQSLEQAQIQQEKKNMYELQKLNSWDVFTNWL-Z

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in which:

amino acid residues are presented by the single-letter code;

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X comprises an amino group, an acetyl group, a 9-fluoromethoxymethyl-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

20

Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

13. A peptide having a formula selected from the group consisting of:

X-YTS-Z  
 X-YTSV-Z  
 25 X-YTSVI-Z  
 X-YTSVIT-Z  
 X-YTSVITI-Z  
 X-YTSVITIE-Z  
 X-YTSVITIEL-Z  
 X-YTSVITIELS-Z  
 X-YTSVITIELSN-Z  
 X-YTSVITIELSNI-Z  
 30 X-YTSVITIELSNIK-Z  
 X-YTSVITIELSNIKE-Z  
 X-YTSVITIELSNIKEN-Z  
 X-YTSVITIELSNIKENK-Z  
 X-YTSVITIELSNIKENKC-Z  
 X-YTSVITIELSNIKENKCN-Z  
 X-YTSVITIELSNIKENKCNG-Z  
 35 X-YTSVITIELSNIKENKCNGT-Z  
 X-YTSVITIELSNIKENKCNGTD-Z

X-YTSVITIELSNIKENKCNGTDA-Z  
 X-YTSVITIELSNIKENKCNGTDAK-Z  
 X-YTSVITIELSNIKENKCNGTDAKV-Z  
 X-YTSVITIELSNIKENKCNGTDAKVK-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKL-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLI-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIK-Z  
 5 X-YTSVITIELSNIKENKCNGTDAKVKLIQ-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQE-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQEL-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELD-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDK-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKY-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYK-Z  
 10 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKN-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNA-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAV-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTE-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTEL-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQ-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQL-Z  
 15 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQQL-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQQLM-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQQLMQ-Z  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQQLMQS-Z and  
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQQLMQST-Z, or

X-QST-Z  
 20 X-MQST-Z  
 X-LMQST-Z  
 X-LLMQST-Z  
 X-QLLMQST-Z  
 X-LQLLMQST-Z  
 X-ELQLLMQST-Z  
 X-TELQLLMQST-Z  
 X-VTELQLLMQST-Z  
 25 X-AVTELQLLMQST-Z  
 X-NAVTELQLLMQST-Z  
 X-KNAVTELQLLMQST-Z  
 X-YKNAVTELQLLMQST-Z  
 X-KYKNAVTELQLLMQST-Z  
 X-DKYKNAVTELQLLMQST-Z  
 X-LDKYKNAVTELQLLMQST-Z  
 30 X-ELDKYKNAVTELQLLMQST-Z  
 X-QELDKYKNAVTELQLLMQST-Z  
 X-KQELDKYKNAVTELQLLMQST-Z  
 X-IKQELDKYKNAVTELQLLMQST-Z  
 X-LIKQELDKYKNAVTELQLLMQST-Z  
 X-KLIKQELDKYKNAVTELQLLMQST-Z  
 X-VKLIKQELDKYKNAVTELQLLMQST-Z  
 X-KVKLIKQELDKYKNAVTELQLLMQST-Z  
 35 X-AKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-DAKVKLIKQELDKYKNAVTELQLLMQST-Z

X-TDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-GTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-NGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-CNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-KCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-NKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 5 X-ENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-IKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-NIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-LSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-ELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 10 X-TIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-ITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z  
 X-TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z

in which:

15 amino acid residues are presented by the single-  
 letter code;  
 X comprises an amino group, an acetyl group, a 9-  
 fluoromethoxymethyl-carbonyl group, a  
 hydrophobic group, or a macromolecule  
 20 carrier group;  
 Z comprises a carboxyl group, an amido group, a  
 hydrophobic group, or a macromolecular  
 carrier group.

25 14. A peptide having a formula selected from the  
 group consisting of:

X-FYD-Z  
 X-FYDP-Z  
 X-FYDPL-Z  
 X-FYDPLV-Z  
 X-FYDPLVF-Z  
 30 X-FYDPLVFP-Z  
 X-FYDPLVFPS-Z  
 X-FYDPLVFPSD-Z  
 X-FYDPLVFPSDE-Z  
 X-FYDPLVFPSDEF-Z  
 X-FYDPLVFPSDEFD-Z  
 X-FYDPLVFPSDEFDA-Z  
 X-FYDPLVFPSDEFDAS-Z  
 35 X-FYDPLVFPSDEFDASI-Z

X-FYDPLVFPSDEFDASIS-Z  
 X-FYDPLVFPSDEFDASISQ-Z  
 X-FYDPLVFPSDEFDASISQV-Z  
 X-FYDPLVFPSDEFDASISQVN-Z  
 X-FYDPLVFPSDEFDASISQVNE-Z  
 X-FYDPLVFPSDEFDASISQVNEK-Z  
 X-FYDPLVFPSDEFDASISQVNEKI-Z  
 5 X-FYDPLVFPSDEFDASISQVNEKIN-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQ-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQS-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSL-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLA-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAF-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFI-Z  
 10 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIR-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRK-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKS-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSD-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDE-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-Z  
 X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z, or  
  
 15 X-DELL-Z  
 X-SDELL-Z  
 X-KSDELL-Z  
 X-RKSDELL-Z  
 X-IRKSDELL-Z  
 X-FIRKSDELL-Z  
 X-AFIRKSDELL-Z  
 20 X-LAFIRKSDELL-Z  
 X-SLAFIRKSDELL-Z  
 X-QSLAFIRKSDELL-Z  
 X-NQSLAFIRKSDELL-Z  
 X-INQSLAFIRKSDELL-Z  
 X-KINQSLAFIRKSDELL-Z  
 X-EKINQSLAFIRKSDELL-Z  
 X-NEKINQSLAFIRKSDELL-Z  
 25 X-VNEKINQSLAFIRKSDELL-Z  
 X-QVNEKINQSLAFIRKSDELL-Z  
 X-SQVNEKINQSLAFIRKSDELL-Z  
 X-ISQVNEKINQSLAFIRKSDELL-Z  
 X-SISQVNEKINQSLAFIRKSDELL-Z  
 X-ASISQVNEKINQSLAFIRKSDELL-Z  
 X-DASISQVNEKINQSLAFIRKSDELL-Z  
 X-FDASISQVNEKINQSLAFIRKSDELL-Z  
 30 X-EFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-DEFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-SDEFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-PSDEFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-FPSDEFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-VFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-LVFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z  
 35 X-PLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z  
 X-DPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z



X-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z

in which:

amino acid residues are presented by the single-letter code;

5

X comprises an amino group, an acetyl group, a 9-fluoromethoxymethyl-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

10

Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

15. A peptide having a formula selected from the group consisting of:

15

X-ITL-Z

X-ITLN-Z

X-ITLNN-Z

X-ITLNNS-Z

X-ITLNNSV-Z

X-ITLNNSVA-Z

20

X-ITLNNSVAL-Z

X-ITLNNSVALD-Z

X-ITLNNSVALDP-Z

X-ITLNNSVALDPI-Z

X-ITLNNSVALDPID-Z

X-ITLNNSVALDPIDI-Z

X-ITLNNSVALDPIDIS-Z

X-ITLNNSVALDPIDISI-Z

25

X-ITLNNSVALDPIDISIE-Z

X-ITLNNSVALDPIDISIEL-Z

X-ITLNNSVALDPIDISIELN-Z

X-ITLNNSVALDPIDISIELNK-Z

X-ITLNNSVALDPIDISIELNKA-Z

X-ITLNNSVALDPIDISIELNKAK-Z

X-ITLNNSVALDPIDISIELNKAKS-Z

X-ITLNNSVALDPIDISIELNKAKSD-Z

30

X-ITLNNSVALDPIDISIELNKAKSDL-Z

X-ITLNNSVALDPIDISIELNKAKSDLE-Z

X-ITLNNSVALDPIDISIELNKAKSDLEE-Z

X-ITLNNSVALDPIDISIELNKAKSDLEES-Z

X-ITLNNSVALDPIDISIELNKAKSDLEESK-Z

X-ITLNNSVALDPIDISIELNKAKSDLEESKE-Z

X-ITLNNSVALDPIDISIELNKAKSDLEESKEW-Z

35

X-ITLNNSVALDPIDISIELNKAKSDLEESKEWI-Z

X-ITLNNSVALDPIDISIELNKAKSDLEESKEWIR-Z

X-ITLNNVALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-ITLNNVALDPIDISIELNKAUSDLEESKEWIRRS-Z, or

5 X-RRS-Z  
 X-IRRS-Z  
 X-WIRRS-Z  
 X-EWIRRS-Z  
 X-KEWIRRS-Z  
 X-SKEWIRRS-Z  
 X-ESKEWIRRS-Z  
 X-EESKEWIRRS-Z  
 X-LEESKEWIRRS-Z  
 X-DLEESKEWIRRS-Z  
 X-SDLEESKEWIRRS-Z  
 10 X-KSDLEESKEWIRRS-Z  
 X-AKSDLEESKEWIRRS-Z  
 X-KAKSDLEESKEWIRRS-Z  
 X-NKAKSDLEESKEWIRRS-Z  
 X-LNKAUSDLEESKEWIRRS-Z  
 X-ELNKAUSDLEESKEWIRRS-Z  
 X-IELNKAUSDLEESKEWIRRS-Z  
 X-SIELNKAUSDLEESKEWIRRS-Z  
 15 X-ISIELNKAUSDLEESKEWIRRS-Z  
 X-DISIELNKAUSDLEESKEWIRRS-Z  
 X-IDISIELNKAUSDLEESKEWIRRS-Z  
 X-PIDISIELNKAUSDLEESKEWIRRS-Z  
 X-DPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-LDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-ALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 20 X-VALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-SVALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-NSVALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-NNSVALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-LNNSVALDPIDISIELNKAUSDLEESKEWIRRS-Z  
 X-TLNNVALDPIDISIELNKAUSDLEESKEWIRRS-Z

in which:

25 amino acid residues are presented by the single-letter code;  
 X comprises an amino group, an acetyl group, a 9-fluoromethoxymethyl-carbonyl group, a hydrophobic group, or a macromolecule  
 30 carrier group;  
 Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

35

16. A peptide having a formula selected from the group consisting of:

- X-ALG-Z  
 X-ALGV-Z  
 X-ALGVA-Z  
 X-ALGVAT-Z  
 5 X-ALGVATS-Z  
 X-ALGVATSA-Z  
 X-ALGVATSAQ-Z  
 X-ALGVATSAQI-Z  
 X-ALGVATSAQIT-Z  
 X-ALGVATSAQITA-Z  
 X-ALGVATSAQITAA-Z  
 10 X-ALGVATSAQITAAV-Z  
 X-ALGVATSAQITAAVA-Z  
 X-ALGVATSAQITAVAL-Z  
 X-ALGVATSAQITAVALV-Z  
 X-ALGVATSAQITAVALVE-Z  
 X-ALGVATSAQITAVALVEA-Z  
 X-ALGVATSAQITAVALVEAK-Z  
 X-ALGVATSAQITAVALVEAKQ-Z  
 15 X-ALGVATSAQITAVALVEAKQA-Z  
 X-ALGVATSAQITAVALVEAKQAR-Z  
 X-ALGVATSAQITAVALVEAKQARS-Z  
 X-ALGVATSAQITAVALVEAKQARSD-Z  
 X-ALGVATSAQITAVALVEAKQARSDI-Z  
 X-ALGVATSAQITAVALVEAKQARSDIE-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEK-Z  
 20 X-ALGVATSAQITAVALVEAKQARSDIEKL-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEKLK-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEKLKE-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEKLKEA-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEKLKEAI-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEKLKEAIR-Z  
 X-ALGVATSAQITAVALVEAKQARSDIEKLKEAIRD-Z, or  
 25 X-IRD-Z  
 X-AIRD-Z  
 X-EAIRD-Z  
 X-KEAIRD-Z  
 X-LKEAIRD-Z  
 X-KLKEAIRD-Z  
 X-EKLKEAIRD-Z  
 30 X-IEKLKEAIRD-Z  
 X-DIEKLKEAIRD-Z  
 X-SDIEKLKEAIRD-Z  
 X-RSDIEKLKEAIRD-Z  
 X-ARSDIEKLKEAIRD-Z  
 X-QARSDIEKLKEAIRD-Z  
 X-KQARSDIEKLKEAIRD-Z  
 X-AKQARSDIEKLKEAIRD-Z  
 35 X-EAKQARSDIEKLKEAIRD-Z  
 X-VEAKQARSDIEKLKEAIRD-Z

X-LVEAKQARSDIEKLKEAIRD-Z  
 X-ALVEAKQARSDIEKLKEAIRD-Z  
 X-VALVEAKQARSDIEKLKEAIRD-Z  
 X-AVALVEAKQARSDIEKLKEAIRD-Z  
 X-AAVALVEAKQARSDIEKLKEAIRD-Z  
 X-TAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-ITAAVALVEAKQARSDIEKLKEAIRD-Z  
 5 X-QITAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-AQITAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-SAQITAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-TSAQITAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-ATSAQITAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-VATSAQITAAVALVEAKQARSDIEKLKEAIRD-Z  
 X-GVATSAQITAAVALVEAKQARSDIEKLKEAIRD-Z  
 10 X-LGVATSAQITAAVALVEAKQARSDIEKLKEAIRD-Z

in which:

amino acid residues are presented by the single-letter code;

15 X comprises an amino group, an acetyl group, a 9-fluoromethyloxymethyl-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

20 Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

17. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein X is a hydrophobic group.

25 18. The peptide of Claim 17 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

30 19. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein Z is a hydrophobic group.

20. The peptide of Claim 19 wherein the hydrophobic group Z is t-butyloxycarbonyl.

35

21. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein X is a macromolecular carrier group.

22. The peptide of Claim 21 wherein the macromolecular carrier group is a lipid-fatty acid conjugate, a polyethylene glycol, or a carbohydrate moiety.

23. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein Z is a macromolecular carrier group.

24. The peptide of Claim 23 wherein the macromolecular carrier group Z is a lipid-fatty acid conjugate, a polyethylene glycol, or a carbohydrate moiety.

25. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein at least one bond linking adjacent amino acid residues is a non-peptide bond.

26. The peptide of Claim 25 wherein the non-peptide bond is an inino, ester, hydrazine, semicarbazide, or azo bond.

27. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein at least one amino acid residue is in a D-isomer configuration.

28. The peptide of Claim 11, 12, 13, 14, 15 or 16 further comprising at least one amino acid insertion.

29. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein the amino acid insertion is between 1 and 15 amino acid residues.

30. The peptide of Claim 11, 12, 13, 14, 15 or 16 having at least one less amino acid residue, wherein the amino acid residue(s) represents an amino acid deletion, and wherein the peptide comprises at least three amino acid residues.

5

31. The peptide of Claim 11, 12, 13, 14, 15 or 16 further comprising at least one amino acid substitution wherein a first amino acid residue is substituted for a second, different amino acid residue.

10

32. The peptide of Claim 31 wherein the amino acid substitution is a conserved substitution.

15

33. The peptide of Claim 31 wherein the amino acid substitution is a non-conserved substitution.

34. A method for the inhibition of transmission of an enveloped virus to a cell, comprising contacting the cell with an effective concentration of the peptide of Claim 1 for an effective period of time so that no infection of the cell by the virus occurs.

20

35. A method for neutralizing an enveloped virus in a host, comprising administering to the host an effective concentration of the peptide of Claim 1 so that the host raises an immune response sufficient to neutralize the virus, and viral infection of uninfected cells in the host is inhibited.

25

30

36. A method for neutralizing an enveloped virus in a host, comprising administering to the host an effective concentration of an antibody raised against the peptide of Claim 1 so that viral infection of uninfected cells in the host is inhibited.

35

37. A method for the detection of an enveloped virus comprising:

contacting a viral isolate with an effective concentration of the peptide of Claim 1 for an effective amount of time so that viral infectivity is inhibited; and

assaying the viral isolate for viral enzyme activity.

38. A method for the inhibition of transmission of an HIV retrovirus to a cell, comprising contacting the cell with an effective concentration of the peptide of Claim 11 or 12 for an effective period of time so that no infection of the cell by the retrovirus occurs.

39. A method for neutralizing an HIV retrovirus in a host, comprising administering to the host an effective concentration of the peptide of Claim 11 or 12 so that the host raises an immune response sufficient to neutralize the HIV retrovirus, and HIV infection of uninfected cells in the host is inhibited.

40. A method for neutralizing an HIV retrovirus in a host, comprising administering to the host an effective concentration of an antibody raised against the peptide of Claim 11 or 12 so that HIV infection of uninfected cells in the host is inhibited.

41. A method for the detection of HIV, comprising:

contacting a viral isolate with an effective concentration of the peptide of Claim 11 or 12 for an effective amount of time so that HIV viral infectivity is inhibited; and

assaying the viral isolate for retroviral enzyme activity.

42. A method for the inhibition of transmission of a respiratory syncytial virus to a cell, comprising  
5 contacting the cell with an effective concentration of the peptide of Claim 13 or 14 for an effective period of time so that no infection of the cell by the virus occurs.

10 43. A method for neutralizing a respiratory syncytial virus in a host, comprising administering to the host an effective concentration of the peptide of Claim 13 or 14 so that the host raises an immune  
15 response sufficient to neutralize the virus, and respiratory syncytial virus infection of uninfected cells in the host is inhibited.

20 44. A method for neutralizing a respiratory syncytial virus in a host comprising administering to the host an effective concentration of an antibody raised against the peptide of Claim 13 or 14 so that respiratory syncytial virus infection of uninfected cells in the host is inhibited.

25 45. A method for the detection of respiratory syncytial virus comprising:  
contacting a viral isolate with an effective concentration of the peptide of Claim 13 or 14 for an effective amount of time so that respiratory syncytial  
30 viral infectivity is inhibited; and  
assaying the viral isolate for respiratory syncytial virus enzyme activity.

35 46. A method for the inhibition of transmission of a parainfluenza virus to a cell comprising,



contacting the cell with an effective concentration of the peptide of Claim 15 or 16 for an effective period of time so that no infection of the cell by the virus occurs.

5           47. A method for neutralizing a parainfluenza virus in a host, comprising administering to the host an effective concentration of the peptide of Claim 15 or 16 so that the host raises an immune response  
10           sufficient to neutralize the virus, and parainfluenza infection of uninfected cells in the host is inhibited.

          48. A method for neutralizing a parainfluenza virus in a host comprising administering to the host  
15           an effective concentration of an antibody raised against the peptide of Claim 15 or 16 so that parainfluenza infection of uninfected cells in the host is inhibited.

20           49. A method for the detection of parainfluenza virus comprising:

          contacting a viral isolate with an effective concentration of the peptide of Claim 15 or 16 for an effective amount of time so that parainfluenza viral  
25           infectivity is inhibited; and

          assaying the viral isolate for parainfluenza virus enzyme activity.

30

35

HIV1LAI (DP-178; SEQ ID:1)	YTSLIHSLIEESQNQKEKNEQELLELDKWASLWNWF
HIV1SF2 (DP-185; SEQ ID:3)	YTNTIYNLLEESQNQKEKNEQELLELDKWASLWNWF
HIV1RF (SEQ ID:4)	YTGIIYNLLEESQNQKEKNEQELLELDKWANLWNWF
HIV1MN (SEQ ID:5)	YTSLIYSLLEKSTQKEKNEQELLELDKWASLWNWF
HIV2ROD (SEQ ID:6)	LEANISKSEQAQIQKEKNMYELQKLSWDIFGNWF
HIV2NIHZ (SEQ ID:7)	LEANISQSLEQAQIQKEKNMYELQKLSWDVFTNWL
DP180 (SEQ ID:2)	SSESFTLLEQWNNMKLQLAEQWLEQINEKHYLEDIS
DP118 (SEQ ID:10)	QQLLDWVKRQQEMLRLTVWGTKNLQARVTAIEKYLKDQ
DP125 (SEQ ID:8)	CGGNLLRAIEAQQHLLQLTVWG IKQLQARILAVERYLKDQ
DP116 (SEQ ID:9)	LQARILAVERYLKDQQQ

FIG.1

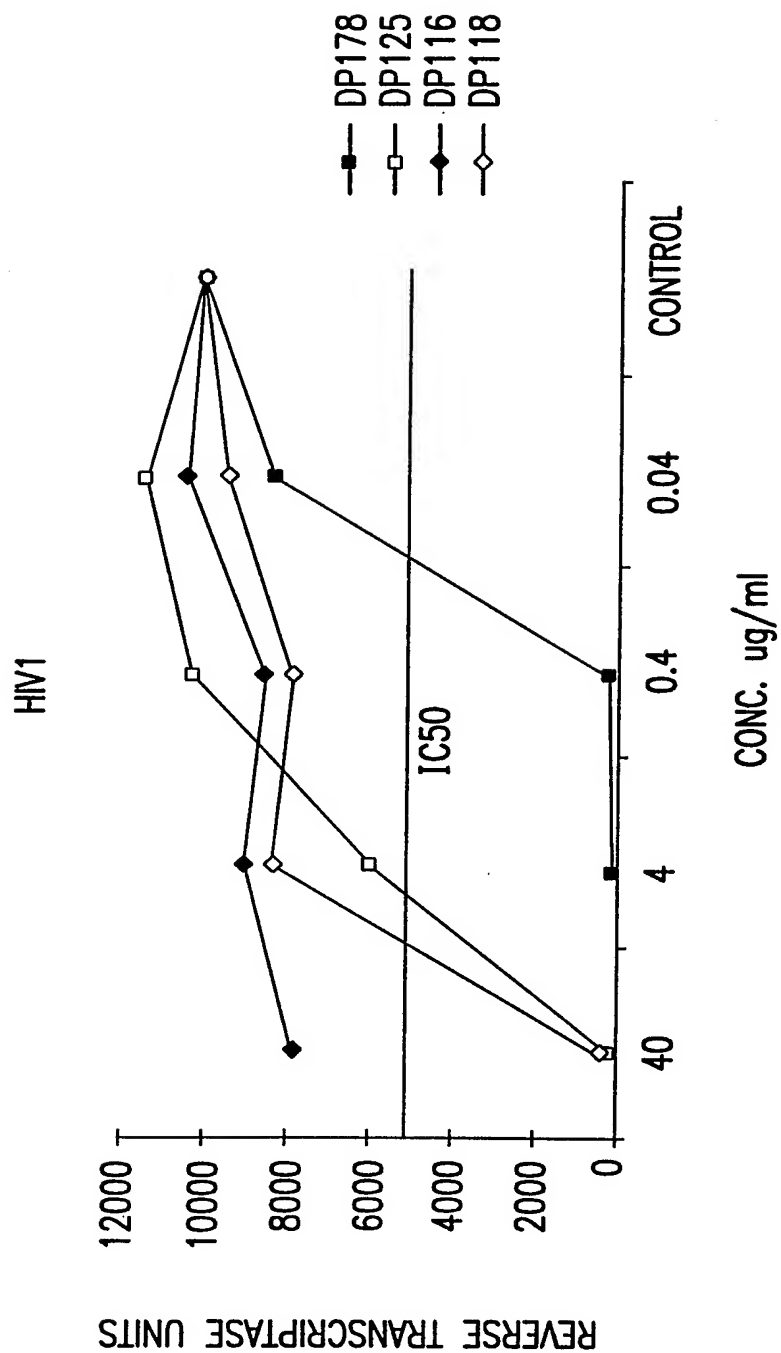


FIG.2

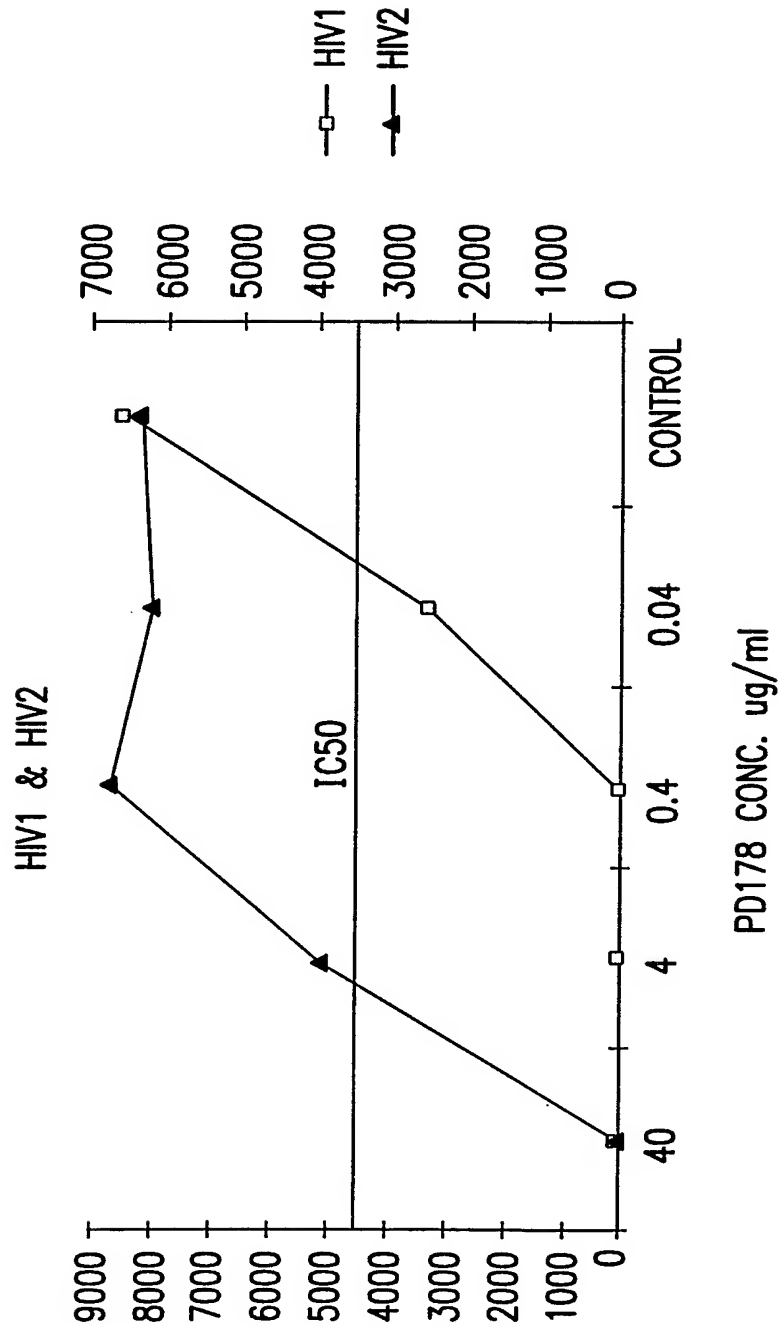


FIG.3

Number of Syncytia/well: concentration in $\mu\text{g/ml}$ (micrograms/ml)									
DP178	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	0	0	0	0	0	0	67
HIV1MN	0	0	0	0	0	ND	ND	ND	34
HIV1RF	0	0	0	0	0	ND	ND	ND	65
HIV1SF2	0	0	0	0	0	ND	ND	ND	58
DP125	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	54	69	80	75	79	82	67
HIV1MN	0	0	30	36	ND	ND	ND	ND	34
HIV1RF	0	0	67	63	ND	ND	ND	ND	65
HIV1SF2	0	0	9	66	ND	ND	ND	ND	58
DP116	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	75	ND	ND	ND	ND	ND	ND	ND	67
HIV1MN	35	ND	ND	ND	ND	ND	ND	ND	34
HIV1RF	81	ND	ND	ND	ND	ND	ND	ND	65
HIV1SF2	81	ND	ND	ND	ND	ND	ND	ND	58

FIG.4A

DP180	40	20	10	5	2.5	1.25	0.625	0.3125	Control
<i>Syncytia</i>									
HIV1LAT	50	>45	>45	>45	>45	>45	>45	>45	58
DP185	40	20	10	5	2.5	1.25	0.625	0.3125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	0	0	0	0	0	ND	60

FIG.4B  
4 / 31

<u>HIV1</u>								
Number of Syncytia/well: concentration in ng/ml (nanograms/ml)								
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV1	0	0	0	0	0	14	20	48
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV1	ND	48	ND	ND	ND	ND	ND	ND
<u>HIV2</u>								
Number of Syncytia/well: concentration in $\mu$ g/ml (micrograms/ml)								
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV2	50	54	55	57	63	77	78	76
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV2	ND	58	ND	ND	ND	ND	ND	ND

FIG.5

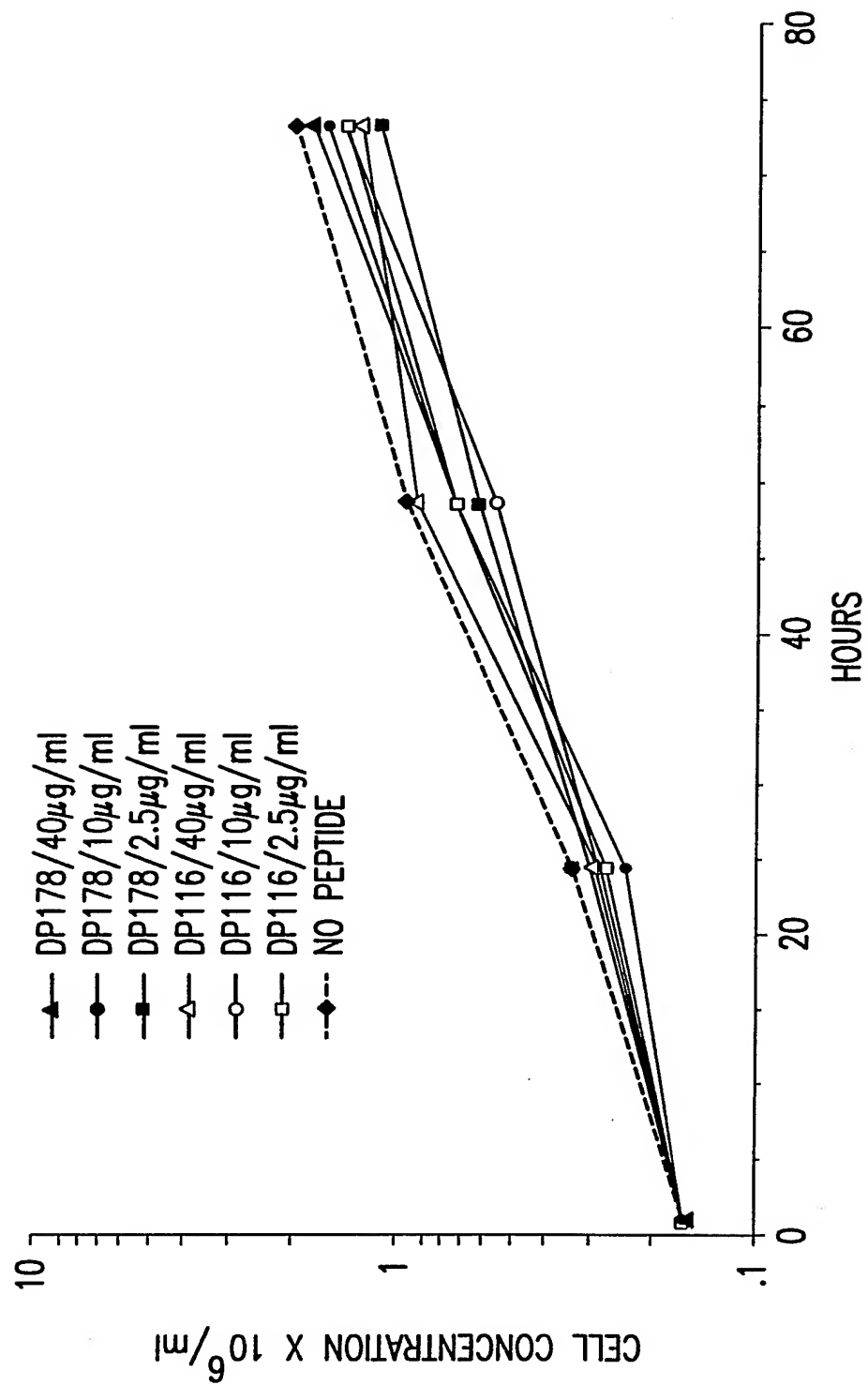


FIG.6

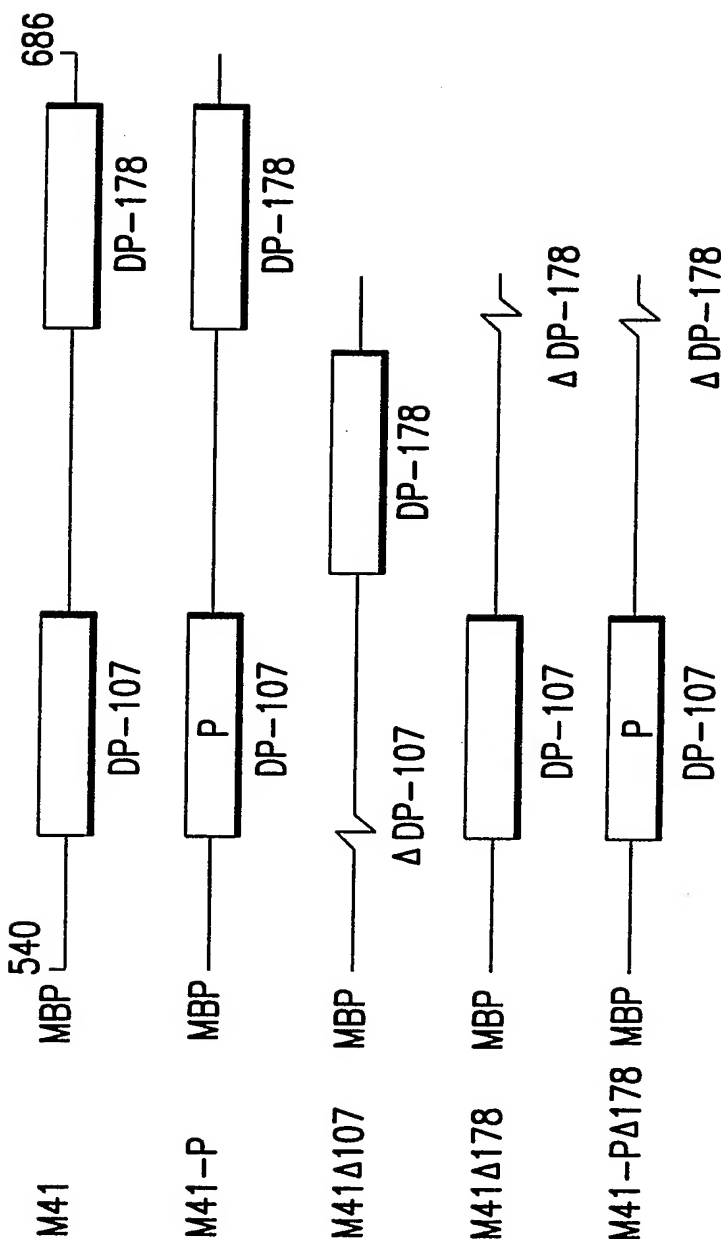
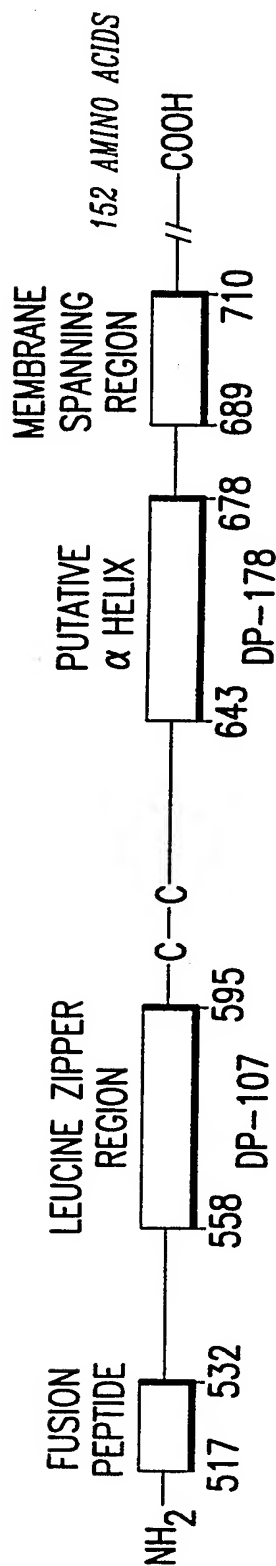


FIG.7



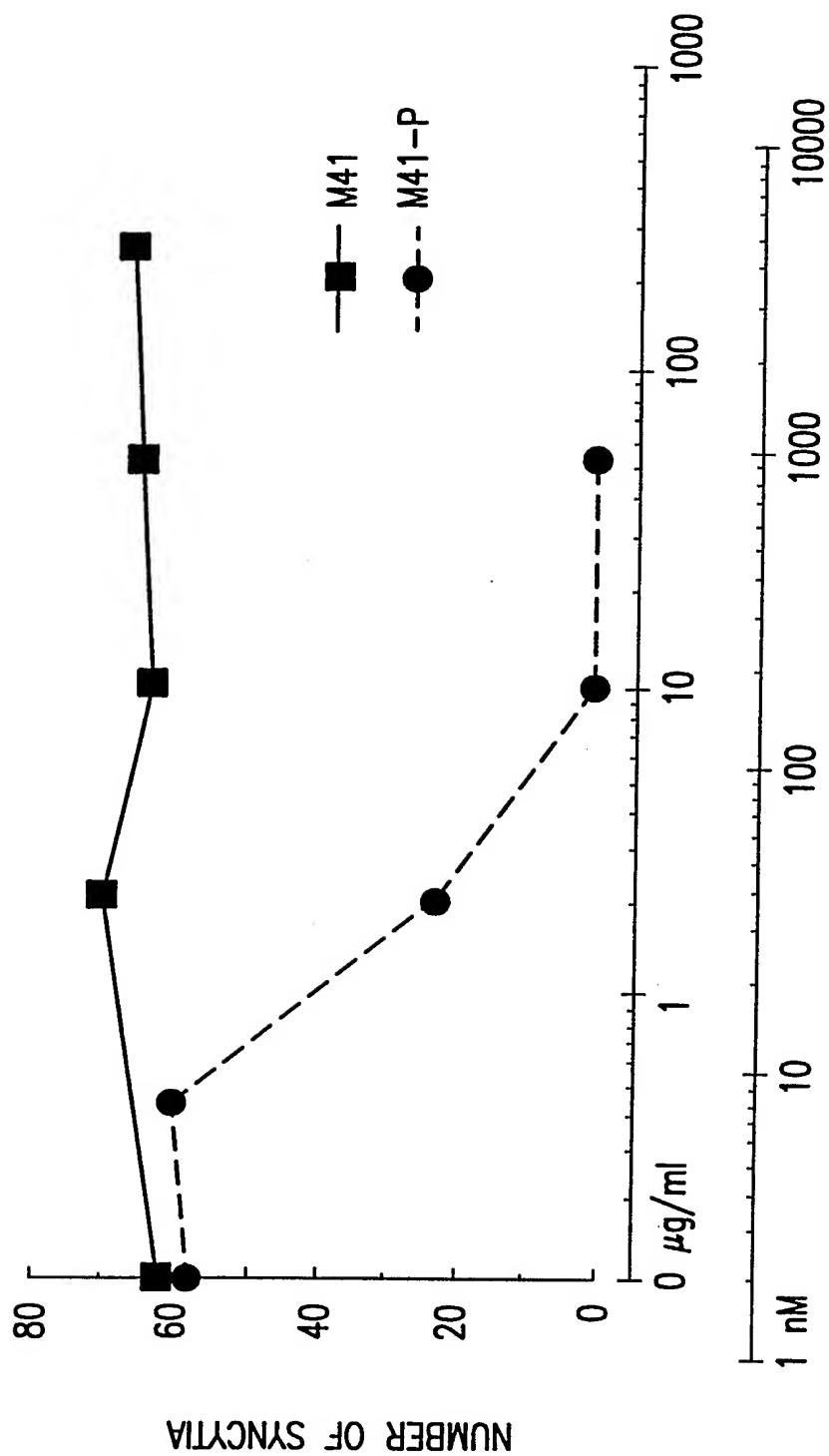


FIG.8

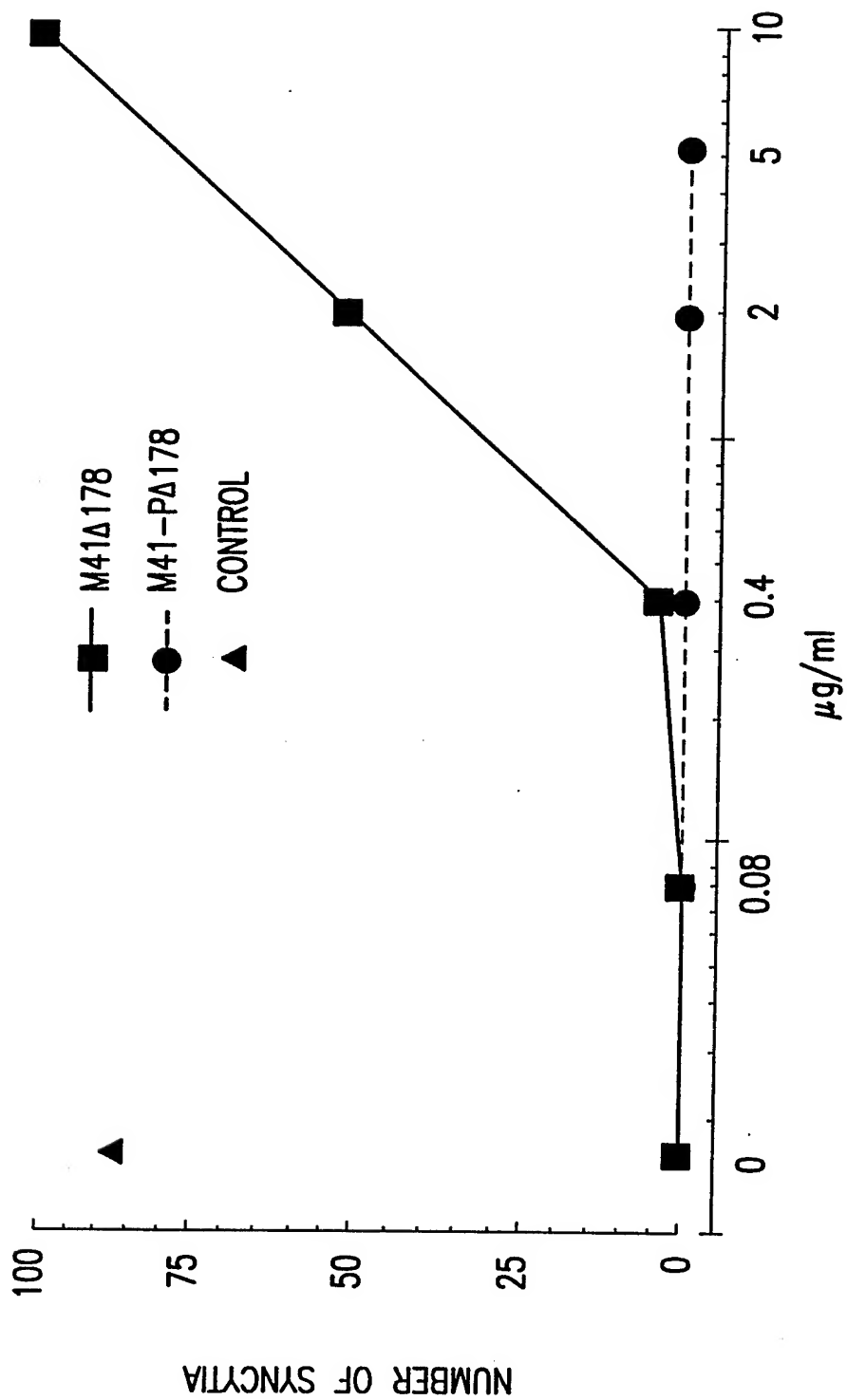


FIG.9

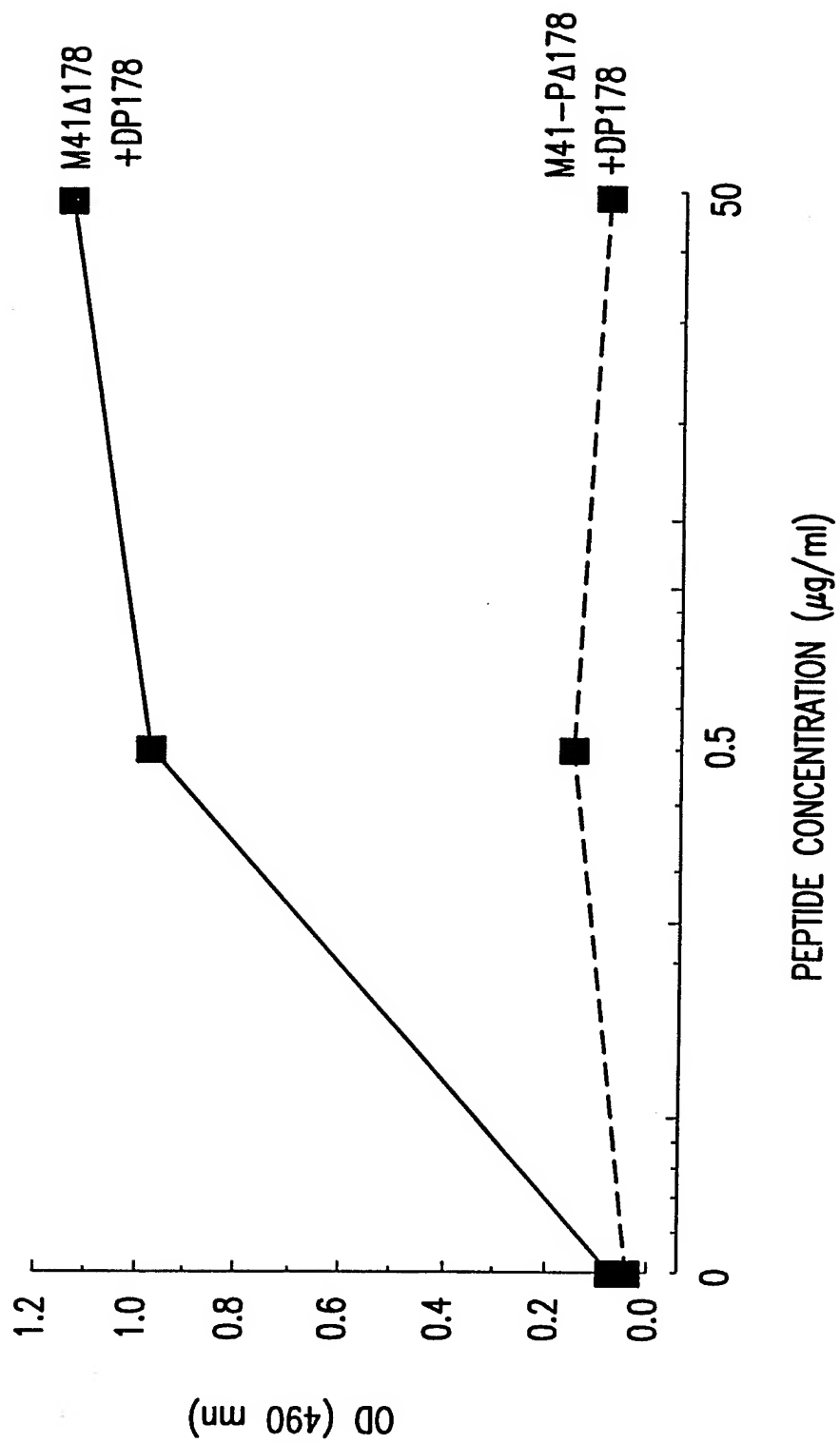


FIG.10

10 / 31

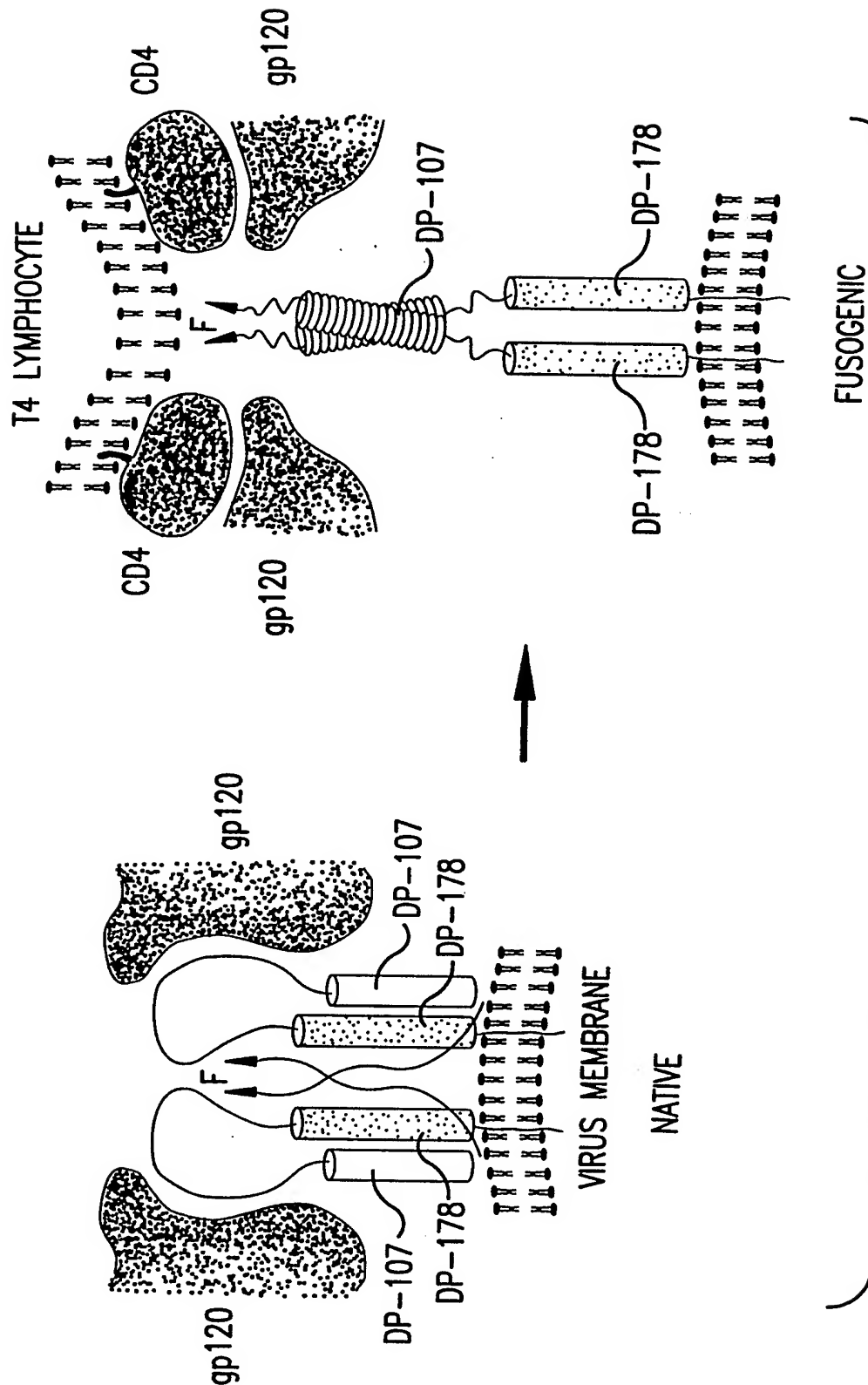


FIG. 11A

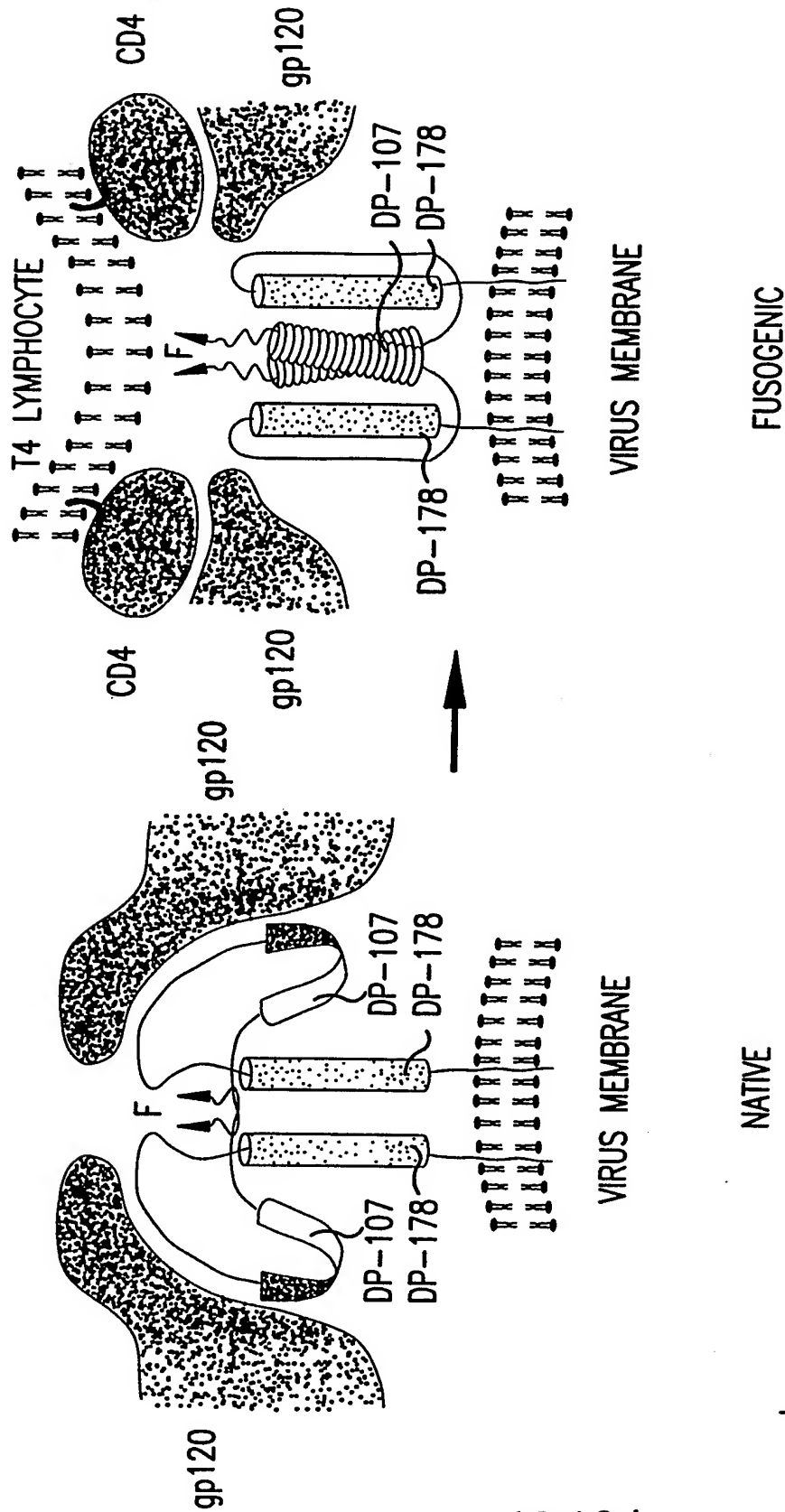


FIG.11B



Sequence	Positions																Motifs																	
	A	D	A	A	D	A	D	A	D	A	D	A	D	A	D																			
DP-107 (env_hv1bru)L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	A	D			[ ILQT ] {CFIMPSTY}			
DP-107 (env_hv1bru)L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	[ ILQTV ] {CDFIMPST}		
DP-107 (env_hv1bru)L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	[ ILQTV ] {CDFIMPST}		
DP-107 (env_hv1bru)L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I						[ EKLNV ] {CDFKMPSVY}		
DP-107 (env_hv1bru)L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	[ EKLNV ] {CFKMPS}		
DP-107 (env_hv1bru)L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	[ EKLNV ] {CFKMPS}		
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K				[ EKLQY ] {ACFGMPRVWY}		
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	[ EKLQWY ] {CFGMPRVY}	
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	[ EFKLQWY ] {CFGMPRVY}	
DP-178 (env_hv1bru)Y1=D		Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K				[ EILNQSY ] {ACFGMPRVWY}	
DP-178 (env_hv1bru)Y1=D		Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	[ EILNQSWY ] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=D		Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	[ EFILNQSWY ] {CFGMPRVY}

FIG.13

Sequence	Positions												Parent Motif	Hybrid Motif																									
	A	D	A	D	A	D	A	D	A	D	A	D																											
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L			[LMNV] {CFGIMPSTW}									
DP-107 (env_hv1bru)L1=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I			{ILQT} {CFIMPSTY}	[ILMNQTV] {CFIMPT}								
DP-107 (env_hv1bru)L1=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	{CDFIMPST}	[ILMNQTV] {CFIMPT}			
DP-107 (env_hv1bru)L1=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	{CDFIMPST}	[ILMNQTV] {CFIMPT}
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I							[EKLNV] {CDFKMPSTVY}	[EKLMNQV] {CFMP}				
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L			[EKLNV] {CFKMPST}	[EKLMNQV] {CFMP}	
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[EKLNV] {CFKMPST}	[EKLMNQV] {CFMP}

**FIG. 14**



Sequence	Positions																								Parent Motif	Hybrid Motif																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	

**FIG. 15**

Sequence	Positions																Parent Motif	Hybrid Motif																						
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D																								
DP-107 (env_hv1bru) L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	A	V	E	R	Y	L	K	D	Q	[ILQTV] {CDFIMPST}								
DP-107 (env_hv1bru) L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	A	V	E	R	Y	L	K	D	Q	[EKLQV] {CFKMPS}								
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFKLQWY] {CFGMPRVY}				
DP-178 (env_hv1bru) Y1=D					Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFILQSWY] {CFGMPRVY}
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	F	S	E	V	E	G	R	I	Q	D	L	E	K	Y										[FILTV] {ACFLMPTVW}		

FIG.16

Sequence	Positions												Parent Motif	Hybrid Motif				
	A	D	A	D	A	D	A	D	A	D	A	D						
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	[LMNV] {CFGIMPTW}		
DP-107 (env_hv1bru)L1=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	[ILQTV] {CDFIMPST}	
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	M	S	L	I	E	E	S	Q	N	Q	Q	[EFKLQWY] {CFGMPRVY}	[EFIKLMNQSTWVY] {CFMP}
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L1=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	[ILQTV] {CDFIMPST}	
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	[EFILNQSIVY] {CFGMPRVY}	[EFILNQRSTWVY] {CFMP}
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	[EKLQV] {CFKIPS}	
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	[EFKLQWY] {CFGMPRVY}	[EFKLNQWVY] {CFMP}
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	[EKLQV] {CFKIPS}	
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	[EFILNQSIVY] {CFGMPRVY}	[EFIKLMNQSTWVY] {CFMP}

FIG.17

Sequence	Positions												Parent Motif	Hybrid Motif
A	D	A	D	A	D	A	D	A	D	A	D	A	D	
GCN4 (gcn4 yeast)	MKQL	EDKV	EEL	LSKN	YHLE	NEVAR	LKKL						[LMNV] {CFGIMPWTW}	
DP-107 (env_hv1bru)L1=D	NNL	LRAI	EAQ	HLQL	TVWG	IKQL	QARR	IIL	AVERY	LKDQ			[ILQTV] {CDFIMPST}	
DP-107 (env_hv1bru)L2=D	NNL	LRAI	EAQ	HLQL	TVWG	IKQL	QARR	LAV	ERYL	KDQ			[EKLQV] {CFMPS}	
DP-178 (env_hv1bru)Y1=A	YTSL	IHS	IEES	QNQQ	EKNE	QEL	LELD	WAS	LWN	WF			[EFKLQWY] {CFGMPRVY}	
DP-178 (env_hv1bru)Y1=D	YTSL	IHS	IEES	QNQQ	EKNE	QEL	LELD	WAS	LWN	WF			[EFILNQSWY] {CFGMPRVY}	
C-FOS (fos_human)	TDTL	QAET	DQL	EDEK	SAL	QTEI	IANLL	KE					[IKLT] {CFGIMPVRWY}	
C-JUN (tap1_human)	IARL	EKV	VKT	LKAQ	NSAL	STAN	MLREQ						[AILNV] {CDFCHILPWY}	
C-MYC (myo_human)	EQKL	ISEE	DLL	EKRRE	QQL	KHKL	EQLRNS						[ELR] {ACFGMPWY}	
FLU LOOP 36	IEKT	NEKF	HQI	EKEF	SEVE	GRIQ	DLEKY						[FILTIV] {ACFLMPTWH}	

[AEFIKLMNQSTVWY] {CFP}  
 = {CDGHP} {CFP}

FIG.18

$P-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(1)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(2)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(3)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(4)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(5)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(7)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(8)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(9)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-\{P\}(10)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-X(1,12)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$   
 $P-X(13,23)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$

FIG.19

Fusion ♥ALLMOTI5♥  
 Peptide ♣107x178x4♣  
 ♥.....ELGFLG A AGSTMGARSM TLTVQARQ ♣LLSGIVQQQ DPI07-NNL

LRAIEAQOHL LOLT VWGIKO LOARIL AVER YLKDO-DPI07 QLLG♥♥ IWGC

♥ALLMOTI5♥ ♣107x178x4♣  
 \*LVS Coiled-Coil\*  
 SGKLICT TAVP ♥WNASWS NKSLEQIWNN MTWM \*E ♣WDREINN DPI78-

YTSLIHSL IEESONQOEK NEOELLELDK\* WASLWNWF-DPI78 NI

♦Transmembrane Region♦  
 TNWLWYIK♣ ♦IFIMIVGGLVGLRIVFAVLSIV NRV RQGYS♥ PL

♣P23LZIPC♣  
 SFQTHLPTPR GPDR ♣PEGIEE EGGERDRDRS IRLVNGSLAL IWDDLRLSL♣ CL

♥ALLMOTI5♥ ♣107x178x4♣  
 F ♥SYHRLRDLL LIVTRIVELL GRGW ♣EALKY WWNLLQYWSQ

ELKNSAVSLL NAT♣ AIAVAEG TDRVIEVVQG A♥ CRAIRHIPR

RIRQGLERIL L

FIG. 20

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SUBSTITUTE SHEET (RULE 26)

Fusion ♡ALLMOTIS♡  
 Peptide ♡107x178x4♡  
 ♡.....FLGFL LGVGSALAS GVA ♡VSKVLHLEGEVNKIKSA  
  
 ♡P1&12LZIPC♡  
LLSTNKAVVS LSNGVSVLTS KVLDLKNYID KQ ♡♡ LL ♡PIVKNKQ  
  
 ♡107x178x4♡  
 SC ♡SISNIETV I ♡ EFQOKNNRLLETTREESYNAG ♡ VTPPVSTMLTNSSELLSL  
  
 ♡P1&12LZIPC♡  
 ♡ALLMOTIS♡  
 INDM ♡PI ♡TNDQ KKLMSNNVQI V ♡ RQSYSI ♡ MS IIKEEVLAYV  
  
 VQ ♡ LPLYGVID TPCWKLHTSP LCTTNTKEGS NICLTRTDRG WYCDNAGSVS  
  
 FFPQAETCKV QSNRVFCDTM NSLTLPSEIN LCNVDIFNPK  
  
 YDCKIMTSKT DVSSSVITSL GAIVSCYGKT KCTASNKNRG  
  
 IIKTFSNGCDYVSNKGMDTV SVGNTLYYVN KQEGKSLYVK G  
  
 ♡P7, 12, & 23LZIPC♡  
 ♡107x178x4♡ ♡ALLMOTIS♡  
 EPIINFYDPLVF ♡PSDE ♡FDASISQVNEKINQSLAF ♡I ♡ RKSDELL ♡  
  
 ♡Transmembrane Region ♡  
 HNVNA ♡ GK STTN ♡IMITTIIVHIVILLS LIAVGLLLY ♡ C ♡  
  
 KARSTPVTLS KDQLSGINNI AFSN

FIG. 21

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Fusion  
 Peptide ♡ALLMOTI5♡ ♡107x178x4♡  
 .....FLGFELG ♡AAGTA MGAAA ♡TALTVQSOHLLAGILOQQQKNLLAAV

♡107x178x4♡  
EAQ♡ QQM ♡LKLTIWGVKNLNARVTALEKYLEDOARLN♡ AWG♡ CA

\*LVS Coiled-Coil\*  
 ♡ALLMOTI5♡ ♡107x178x4♡  
 WKQVCHTTVP WQWNNRTPDW ♡NNMT \*WLE ♡WEROISYLEGNTT

♡107x178x4♡  
TOLEEARAQEEKNLD♡ AYOKLSS\* WSDFWSW♡ FDF ♡SKWLN ♦ILK

♦Transmembrane Region♦  
IGELDVLGIGLRLLYTV♦ YS♡ CIARVRQGYSP LSPQIHHP WKGQPDNAEG

PGEGGDKRKN SSEPWQKESG TAEWKS NWCK RL TNWCSISS IWL YNS

♡ALLMOTI5♡  
 ♡CLTL LVHLRSAFQY IQYGLGELKA AAQEAVVALA RLAQNAGYQIWL♡

ACRSAYRA IINSPRRVRQ GLEGILN

FIG. 22



Fusion ♣107x178x4♣  
 Peptide ♡ALLMOTI5♡ \*LVS Coiled-Coil\*  
 .....EAG ♡VVL AGVALGVATA AQITAGIALHQ ♣\*SNLNAQAIQ

SLRTSLEQSNKAIEEIREATOETVIA\* VOGVQDY♣ VNNEL♡ VP

♡ALLMOTI5♡  
 ♣107x178x4♣

AMQHMSCELVGQRLGLRLLRYYTELLSIFGPSLRD ♣P6 & 12LZIPC♣  
 ♣PISA ♣♡EISIQALIIYAL

GGEIHKILEKLGYSSD♣ MIAILES~~R~~GIKTKI♡ THVDLP~~G~~KFIILSISY

♣P1 & 12LZIPC♣  
 ♣PTLSEVKGVIVHRLEAV♣ SYNIGSQEWYTTVPRYIATNGYLISNFDESSCVFVS

ESAICSQNSL YPMSPLLQQC IRGDTSSCAR TLVSGTMGNK FILSKGNIVA

NCASILCKCY STSTINQSP DKLLTFIASD TCPLVEIDGA TIQVGGRQYP

\*LVS Coiled-Coil\*  
 ♡ALLMOTI5♡  
 ♣P12 & 23LZIPC♣

DMVYEGKVAL G ♣PAISLD ♡RL\*DVGTNLGNALKKLDDAKVLI♣

♦Transmembrane Region♦

DSS♣ NOILETVRRS♡\* SFN ♦FGSLLSVPI~~L~~SCTAL ALLLLIYCC♦

K RRYQQTLKQH TKVDPAFKPD LTGTSKSYVR SL

FIG. 23

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SUBSTITUTE SHEET (RULE 26)

Fusion ♥ALLMOTI5♥  
 Peptide ♣107x178x4♣  
 ♥.....FIGAI IGSVALGVA TAAQITAASA LIQANQNAAN ♣ILRLKESITA  
TIEAVHEVTDGLSQLAVA♣ VG KM♥ QQFVNDQFNNTAQELDCIKITQQV  
 ♥ALLMOTI5♥  
 GVELNLYLTELT TV FGPQITSPAL ♥TQLTIQALYNAGGNMDYLLTKLGVG  
 ♣P1 & 12LZIPC♣  
 NNQLSSLIGSGLIT GN♥ ♣PILYDSQT QLLGIQVTLP SVGNLNNMRATYLET  
 LSVST TKGFASALVP KVV TQVGSVI EELDTSYCIE TDLDLYCTRI VTFPMSPGIY  
 SCLNGNTSAC MYSKTEGALT TPYMTLKGSV IANCKMTTCR CADPPGIISQ  
 ♥ALLMOTI5♥  
 ♣107x178x4♣  
 NYGEAVSLID RHSCN ♣♥VLSLD GITRLSGEF DATYQKNISI LDSQVIVTG  
 \*LVS Coiled-Coil\* ♣Trans-  
 \*NLDISTELGNV NNSISNALDK LEESNSKLDK VNVKLTSTSA ♣LIT\* YIA  
membrane Region♦  
LTAISLVCGILSLV♥♣ LACYLMY♦ KQKAQQKTLLWLGNNTLGQMRATTKM

FIG. 24

Fusion                      ♥ALLMOTI5♥  
 Peptide            ♠107x178x4♠      \*LVS Coiled-Coil\*  
 .....EEGGV    ♠IG ♥TIALG \*VATSAQITAAAVALVEAKQARSDIEKLKE

AIRDTNKAVQSVQSSIGNLIVAIKSVQ\* DYVNKE♥♠ IVPSIARLGCEAAG

                         ♥ALLMOTI5♥  
                          ♠107x178x4♠  
 LQLGIALTQH ♠♥YSELTNIEGDNIGSLOEKGIKLOGIASLYRTNITE♥♠

   ♠P5 & 12LZIPC♠  
 IFTTSTVDKYDIYDLLFTESIKVRVIDVDLNDYSITLQVRL ♠PLLTRLNTQIYR

VDSISYNI♠ QNREWYI♠ PLPSHIMTKGAFLGGADVKECIEAFSSYIC

PSDPGFVLNHEMESCLSGNISQCPRTVVKSDIVPRYAFVNGGVVANCITT

TCTCNGIGNRINQPPDQGVKIITHKECNTIGINGMLFNTNKEGTLAFYTP

                         ♥ALLMOTI5♥  
                          ♠107x178x4♠  
                          ♠P6 & 23LZIPC♠  
 NDITLNNSVALD ♠PIDI ♠SIELN ♥KAKSDLEESKEWI♠ RRSNOKL♠

                         ♦Transmembrane Region♦  
DSIGNWHQSSTT    ♦IIIV♠ LIM IIILEFINVT II♦    IIAVKYY♥ R  
 IQKRN RV DQN DKPYVLTNK

FIG. 25

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Fusion  
Peptide  
.....GLFGAI AGFIENGWEGMIDGWYGFRHQNSEGTG

♠107x178x4♠  
♥ALLMOTI5♥  
\*LVS Coiled-Coil\*  
\*Q ♥AADLKST ♠QAAIDQINGKLNRVIEKTNEKTHQIEKEESEVEGRIQ  
  
DLEKYVEDTKIDL\* WSYNAELLYALENQHTI♠ DLT♥ DSEMKNLFEKTR  
  
RQLRENAEEMGNGCFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKG  
  
VELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQRGNIRCNICI

FIG. 26

AV	CD	RSV F2	YTSVITIELSNIKENKCNCTDAKVLIKQELDKYKNAVTELQLLMOST
+	+/+	T-142	YTSVITIELSNIKENKCNCTDAKVLIKQELDKYK
++	+/++	T-143	TSVITIELSNIKENKCNCTDAKVLIKQELDKYKN
+	+/+	T-144	SVTITIELSNIKENKCNCTDAKVLIKQELDKYKNA
-	+/+	T-145	VITIELSNIKENKCNCTDAKVLIKQELDKYKNAV
-	+/-	T-146	ITIELSNIKENKCNCTDAKVLIKQELDKYKNAV
-	-	T-147	TIELSNIKENKCNCTDAKVLIKQELDKYKNAVTE
-	-	T-148	IELSNIKENKCNCTDAKVLIKQELDKYKNAVTEL
-	+/-	T-149	ELSNIKENKCNCTDAKVLIKQELDKYKNAVTELO
-	-	T-150	LSNIKENKCNCTDAKVLIKQELDKYKNAVTELOL
-	+/+	T-151	SNIKENKCNCTDAKVLIKQELDKYKNAVTELOLL
-	+/+	T-152	NIKENKCNCTDAKVLIKQELDKYKNAVTELOLLM
-	+/+	T-153	IKENKCNCTDAKVLIKQELDKYKNAVTELOLLMQ
-	+/+	T-154	KENKCNCTDAKVLIKQELDKYKNAVTELOLLMQS
-	+/+	T-155	ENKCNCTDAKVLIKQELDKYKNAVTELOLLMQST

FIG.27

AV	CD	RSV	
++	+/-	T-67	DEFDASISQWNEKINQSLAF IRKSDELL
		F1-178	GEPIINFYDPLVFPSDEFDASISQWNEKINQSLAF IRKSDELLHNVNAGKSTT
+/-		T-104	IIINFYDPLVFPSDEFDASISQWNEKINQSLAF IRK
+/-		T-105	INFYDPLVFPSDEFDASISQWNEKINQSLAF IRKS
+/-		T-106	NFYDPLVFPSDEFDASISQWNEKINQSLAF IRKSD
+		T-107	FYDPLVFPSDEFDASISQWNEKINQSLAF IRKSDE
++		T-108	YDPLVFPSDEFDASISQWNEKINQSLAF IRKSDEL
++		T-109	DPLVFPSDEFDASISQWNEKINQSLAF IRKSDELL
+		T-110	PLVFPSDEFDASISQWNEKINQSLAF IRKSDELLH
++		T-111	LVFPSDEFDASISQWNEKINQSLAF IRKSDELLHN
++	+/-	T-112	VFPSDEFDASISQWNEKINQSLAF IRKSDELLHNV
++	+/-	T-113	FPSDEFDASISQWNEKINQSLAF IRKSDELLHNVN
++	+/-	T-114	PSDEFDASISQWNEKINQSLAF IRKSDELLHNVNA
++	+/-	T-115	SDEFDASISQWNEKINQSLAF IRKSDELLHNVNAG
++	+/-	T-116	DEFDASISQWNEKINQSLAF IRKSDELLHNVNAGK
++	+/-	T-117	EFDASISQWNEKINQSLAF IRKSDELLHNVNAGKS
++	+/-	T-118	FDASISQWNEKINQSLAF IRKSDELLHNVNAGKST
++	+/-	T-119	DASISQWNEKINQSLAF IRKSDELLHNVNAGKSTT

(T-67 LIKE)

FIG.28

AV	CD	HPF3	178	YTPNDITLNNVALDPIDISIELNKAKSDEESKEWIRRSNQKLDISGNWHQSSTT
-	-	189	YTPNDITLNNVALDPIDISIELNKAKSDEESKE	
-	-	190	TPNDITLNNVALDPIDISIELNKAKSDEESKEW	
-	-	191	PNDITLNNVALDPIDISIELNKAKSDEESKEWI	
-	-	192	NDITLNNVALDPIDISIELNKAKSDEESKEWIR	
-	+/-	193	DTLNNVALDPIDISIELNKAKSDEESKEWIRR	
+/-	+/-	194	ITLNNVALDPIDISIELNKAKSDEESKEWIRRS	
+/-	+/+ +	195	TLNNVALDPIDISIELNKAKSDEESKEWIRRSN	
+	+/+	196	LNNVALDPIDISIELNKAKSDEESKEWIRRSNQ	
+	+/+	197	NNVALDPIDISIELNKAKSDEESKEWIRRSNQK	
+++	+/+	198	NSVALDPIDISIELNKAKSDEESKEWIRRSNQKL	
++	+/+	199	SVALDPIDISIELNKAKSDEESKEWIRRSNQKLD	
-		200	VALDPIDISIELNKAKSDEESKEWIRRSNQKLD	
+++		201	ALDPIDISIELNKAKSDEESKEWIRRSNQKLD	
+++		202	LDPIDISIELNKAKSDEESKEWIRRSNQKLD	
++		203	DPIDISIELNKAKSDEESKEWIRRSNQKLD	
++		204	PIDISIELNKAKSDEESKEWIRRSNQKLD	
+++		205	IDISIELNKAKSDEESKEWIRRSNQKLD	
+		206	DISIELNKAKSDEESKEWIRRSNQKLD	
+		207	ISIELNKAKSDEESKEWIRRSNQKLD	
+		208	SIELNKAKSDEESKEWIRRSNQKLD	
++		209	IELNKAKSDEESKEWIRRSNQKLD	
++		210	ELNKAKSDEESKEWIRRSNQKLD	

FIG.29

CD	HPF3 107	GTIALGVATSAQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA I KSVQDYVNKEIVP
+/+	157	ALGVATSAQITA AVALVEAKQARSDIEKLKEAIRD
+/+	158	LGVATSAQITA AVALVEAKQARSDIEKLKEAIRDT
+/-	159	GVATSAQITA AVALVEAKQARSDIEKLKEAIRDTN
+/+	160	VATSAQITA AVALVEAKQARSDIEKLKEAIRDTNK
+/+	161	ATSAQITA AVALVEAKQARSDIEKLKEAIRDTNKA
+/-	162	TSAQITA AVALVEAKQARSDIEKLKEAIRDTNKAV
+/+	163	SAQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQ
+ /+++	164	AQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQS
+/+	165	QITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSV
+/-	166	ITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQ
+/-	167	TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS
+/-	168	AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS
+/-	169	AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI
+/-	170	VALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIG
+/-	171	ALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGN
+/-	172	LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL
+/-	173	VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI
+ /++	174	EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV
	T-40	AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA
+/++	175	KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA I
+ /+++	176	QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA I K
+/-	177	ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA I K S
+/-	178	RS DIEKLKEAIRDTNKAVQSVQSSIGNLIVA I K S V
-	179	SDIEKLKEAIRDTNKAVQSVQSSIGNLIVA I K S V Q
-	180	DIEKLKEAIRDTNKAVQSVQSSIGNLIVA I K S V Q D
-	181	IEKLKEAIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y
-	182	EKLKEAIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V
+ /++	183	KLKEAIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V N
+ /+++	184	LKEAIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V N K
-	185	KEAIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V N K E
-	186	EAIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V N K E I
-	187	AIRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V N K E I V
-	188	IRDTNKAVQSVQSSIGNLIVA I K S V Q D Y V N K E I V P

FIG.30

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SUBSTITUTE SHEET (RULE 26)



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/05739

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 37/02, 39/12; C12Q 1/70; G01N 33/53

US CL : 424/88, 89; 435/5, 7.1, 7.92-7.95, 974; 530/324-331, 333, 334

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/88, 89; 435/5, 7.1, 7.92-7.95, 974; 530/324-331, 333, 334

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Biosis

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
NONE	NONE	NONE

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 SEPTEMBER 1994

Date of mailing of the international search report

26 SEP 1994

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/05739

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
that the claimed subject matter is directed to mental processes.
2. ☒ Claims Nos.: 13-16 and 42-49  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
because the sequences have not been submitted to the International Searching Authority in electronic form.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.